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(54) Title: METHODS FOR IDENTIFYING THERAPEUTIC TARGETS INVOLVED IN GLUCOSE AND LIPID METABOLISM

(57) Abstract: The identification and evaluation of mRNA and protein targets associated with RNA binding proteins or mRNP complexes is described. In particular, the invention provides methods for identifying RNA binding proteins associated with physiological pathways that participate in glucose and lipid metabolism and mRNAs that exhibit coordinated gene regulation across thoseMpathways. Candidate targets are provided that are useful for the diagnosis or treatment of diseases related to diseases, such as disease related to aberrant glucose and lipid metabolism, such as, for example, obesity, diabetes, and hypoglycemia.

Methods for Identifying Therapeutic Targets Involved in Glucose and Lipid Metabolism

RELATED APPLICATIONS

This application claims priority to and the benefit of U.S.S.N. 60/461,016, filed April 7, 2003, the contents of which are incorporated by reference herein.

FIELD OF THE INVENTION

The invention provides methods and compositions for identifying and characterizing functionally related gene products associated with isolated mRNP complexes. The invention also provides methods and compositions for identifying and characterizing metabolic pathways, such as glucose or lipid metabolic pathways, and therapeutic targets and therapeutics for treating diseases associated with metabolic pathways.

BACKGROUND OF THE INVENTION

Glucose and lipid metabolism are regulated by the coordinated expression of a number of proteins that participate in insulin production, secretion, and action. Beta cells of the pancreas sense increased plasma glucose, lipids, and other nutrients, and activate a cascade of intracellular reactions leading to the controlled release of insulin from storage granules. Insulin, in turn, controls plasma glucose and lipid levels by stimulating glucose uptake into insulin-sensitive tissues (*e.g.e.g.*, skeletal muscle and adipose), lipid metabolism, and inhibiting hepatic glucose production.

Diabetes is a disease characterized by an impairment of insulin action. Type 1 diabetes results from an inability of pancreatic beta cells to produce insulin, forcing patients to take daily insulin injections to control their blood glucose. Type 2 diabetes is a metabolic disorder in which a patient becomes resistant to insulin's actions, leading to hyperglycemia, hyperlipidemia, and hyperinsulinemia. In many cases, Type 2 diabetes is associated with obesity and a sedentary lifestyle. Efforts have been made to establish pancreatic beta cell lines from adult and embryonic stem cells and to engineer pancreatic beta cell-like cell lines in order to study the

metabolic pathways that are activated during development, growth, and maintenance of pancreatic beta cells.

Although some of the cellular pathways involved in glucose and lipid metabolism are understood, a number of regulatory aspects of those pathways have not been fully characterized. The identification of RNAs that are co-regulated with insulin gene expression would provide information about the regulation of genes involved in controlling insulin production and secretion by beta cells of the pancreas. Identification of co-expressed RNAs would also help identify previously unknown components of the insulin signaling pathway and other glucose and/or lipid metabolic pathways in adipocytes, as well as other cells that participate in glucose or lipid metabolism. Identification of the components of glucose and lipid metabolic pathways provides new therapeutic targets for diabetes, obesity, and other diseases characterized by altered glucose or lipid metabolism. A need therefor exists for a sensitive, focused, and efficient method for identifying such functionally related genes, therapeutic targets, and therapeutics.

SUMMARY OF THE INVENTION

The invention exploits the ability of RNA binding proteins to bind and coordinate the expression of functionally and structurally related RNAs. The RNAs bound to a particular RNA binding protein define a cluster of functionally related gene products and may also possess common primary and/or secondary structures that mediate binding to the RNA binding protein. RNA binding proteins and RNAs identified by methods of the invention are useful for elucidating physiological or regulatory pathways, such as glucose or lipid metabolic pathways, including insulin action, insulin resistance, obesity, and diabetes. The RNAs, the genes encoding those RNAs, and proteins identified by the methods of the invention are putative therapeutic targets due to their ability to regulate other genes that participate in, or otherwise modulate, aberrant physiological, metabolic or regulatory pathways in a disease state.

The invention provides a ribonomic profile, and methods for identifying and characterizing a ribonomic profile, including the expression of RNAs, RNA binding proteins, and mRNP complex-associated proteins associated with a particular mRNP complex or set of mRNP complexes. For example, genes participating in a glucose or a lipid metabolic pathway are identified by characterizing the mRNAs associated with a particular mRNP complex known, or determined, to be a participant in the pathway. According to the invention, mRNAs or proteins are classified into biologically relevant subsets on the basis of structural and/or

functional relationships (*e.g.e.g.*, that participate in the same insulin production or secretion pathway, or that facilitate gene expression during growth and development in normal or diseased pancreatic beta cells). In contrast to the static genomics and proteomics approaches to gene characterization and drug discovery, this "ribonomics" approach provides a dynamic snapshot of the flow of genetic information at a given time in the life of a cell or tissue, for example, in a normal or diseased state or in response to an environmental influence, such as glucose or a drug.

In an aspect, the invention provides methods for identifying RNA binding protein, mRNA and protein components of an mRNP complex in cells associated with a physiological process or pathway, by immunoprecipitating an mRNP complex, identifying and comparing the components of the mRNP complex, such as, for example, RNA binding proteins, mRNAs, and other proteins, and validating the biological role of those proteins, or the genes that encode those proteins, in the physiological process or pathway. In an embodiment, the method further includes preparing an RNA binding protein profile, isolating the RNA binding protein, and/or producing antibodies to the RNA binding protein.

In one aspect, the invention provides methods of identifying a therapeutic target related to the treatment of a disease, such as aberrant glucose or lipid metabolism. The protein or RNA levels of at least one component of an isolated mRNA ribonucleoprotein (mRNP) complex in a cell sample is measured and compared to the levels of the protein or RNA levels of the component in a second cell sample. The two cell samples may differ in that one is normal and one is diseased or may differ regarding their state of differentiation. The cell samples may also differ in that one sample is treated with an agent and one sample is not. For example, the cell samples may contain mostly mature adipocytes, preadipocytes, pancreatic beta cells, hepatocytes, skeletal muscle cells, or cardiac muscle cells, or any cell that participates in glucose or insulin metabolism, for example. If the levels of the component in the first sample are different from the levels of the component in the second sample, the component, a nucleic acid that encodes the component (if the component is a protein), or a protein encoded by the component (if the component is a nucleic acid) is a potential therapeutic target for the treatment of a disease related to altered glucose or lipid metabolism. In an embodiment, the component is an RNA binding protein, an RNA, or an mRNP-associated protein.

In an embodiment, the first cell sample has the phenotype of a mature adipocyte and the second cell sample has the phenotype of a preadipocyte. A difference in the expression of a

component of the mRNP complex between the two cell types is indicative that the component participates in a pathway involved in the differentiation from preadipocyte to adipocyte.

In another embodiment, the first cell sample has a disease phenotype related to glucose or lipid metabolism, such as obesity, diabetes, hypoglycemia, glucotoxicity, lipidtoxicity, insulin-resistance, hyperlipidemia, and lipodystrophy, and the second cell sample has a normal phenotype.

In another embodiment, the method has an additional step of treating the sample with an agent prior to measuring the protein or RNA levels of the mRNP complex component, wherein the agent alters the levels of at least one component of a glucose metabolic or a lipid metabolic pathway. In an embodiment, the agent is insulin, glucose, insulin-like growth factor-1 (IGF-1), a β-adrenergic agonist, glucagon-like peptide-1 (GLP-1), fatty acid, a peroxisome proliferator activated receptor (PPAR) ligand, or insulin-like growth factor 2 (IGF-2), RNAi against an RNA binding protein, overexpression of an RNA binding protein, or an enhancer of an RNA binding protein for example. In another embodiment, the agent is a test therapeutic, such as, for example, a nucleic acid, a hormone, an antibody, an antibody fragment, an antigen, a cytokine, a growth factor, a pharmacological agent (*e.g.e.g.*, chemotherapeutic, carcinogenic, or other cell), a chemical composition, a protein, a peptide, and/or a small molecule (*e.g.*, a putative drug).

In an aspect, the invention comprises methods for identifying RNA binding protein, mRNA and protein components of an mRNP complex in cells associated with physiological pathways or processes, for example glucose or lipid metabolism. The method includes the steps of identifying RNA binding proteins enriched in cells, such as, for example, adipocytes or preadipocytes (for example in lean or obese individuals), treating the cells with an agent, such as, for example, insulin or a beta 3 agonist, and identifying the components of the mRNP complex (*e.g.*, functional cluster). In an embodiment, the methods of the invention further include the step of identifying a suitable RNA binding protein for analysis, *e.g.*, an RNA binding protein that participates in the regulation of the physiological pathway or process. In a further embodiment, the method further includes the step of validating the function of the component within the pathway.

In another embodiment, the methods of the invention have a further step of isolating the component, a nucleic acid encoding the component, or a protein encoded by the component. For example, the methods of the invention can identify and isolate an mRNA encoding the RNA binding protein and/or an mRNP complex-associated protein, a gene encoding the RNA binding

protein and/or an mRNP complex-associated protein, an mRNP complex comprising the RNA binding protein and/or an mRNP complex-associated protein, an mRNA associated with the mRNP complex, and a gene encoding the mRNA associated with the mRNP complex. In addition, the invention contemplates identifying other associated RNAs that bind to one or mor components of the mRNP complex. These RNAs include, but are not limited to, microRNA (miRNA), non-coding RNA (ncRNA or snmRNA), ribosomal RNA (rRNA), small interfering RNA (siRNA), small nuclear RNA (snRNA), small nuclear RNA (snoRNA), small temporal RNA (stRNA), and transfer RNA (tRNA).

In an embodiment, the component is an RNA binding protein, such as Polypyrimidine Tract Binding Protein (PTB, also known as RNA binding protein 1 (RBP1)). In another embodiment, the RNA binding protein is selected from the group consisting of the RNA bindin proteins identified in Figures 10-22. These RNAs were subjected to analysis on a microarray containing RNA binding protein genes. These genes and their encoded proteins represent candidate therapeutic targets as well as candidates for RAS™ analysis for elucidation of cellula pathways involved in glucose and lipid metabolism, insulin action, insulin resistance, diabetes and obesity, for example. In an embodiment, the RNA binding protein has a tag (*e.g.e.g.*, HIS (GST) to facilitate affinity purification.

In an embodiment, the component is an mRNA that is associated with a particular RNA binding protein. The mRNA are identified singly or mRNAs are identified *en masse*, *e.g.*, usin arrays containing a number of probes. In an embodiment, the mRNA encodes a kinase, a transporter, a phosphatase, a channel protein, a protease, a receptor, a transcription factor, or a transferase. For example, the protein may be 3-phosphoinositide dependent protein kinase-1; nuclear ubiquitous casein kinase 2; neural receptor protein-tyrosine kinase; MAP-kinase activating death domain; AMP-activated protein kinase beta-2 regulatory subunit; calcium/calmodulin-dependent protein kinase IV; Protein kinase C beta; adenylate kinase 3; mitogen activated protein kinase; kinase 5; 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 2; phosphatidylinositol 4-kinase; Glucokinase; glycogen synthase kinase 3 beta; phosphorylase kinase (gamma 2, testis); protein tyrosine phosphatase (non-receptor type 1); protein tyrosine phosphatase (non-receptor type 5); inositol polyphosphate-5-phosphatase D; Protein tyrosine phosphatase (receptor-type, zeta polypeptide); dual specificity phosphatase 6; protein tyrosine phosphatase (non-receptor type 12); glucose-6-phosphatase (catalytic); 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 2; proton gated cation channel DRASIC; Sodium channel (nonvoltage-gated 1, alpha (epithelial)); calcium channel (voltage-dependent,

alpha2/delta subunit 1); Potassium inwardly-rectifying (channel, subfamily J, member 6); potassium channel regulator 1; calcium channel (voltage-dependent, T type, alpha 1G subunit) cyclic nucleotide-gated cation channel; amiloride-sensitive cation channel 1; potassium inwardly-rectifying channel J14; potassium large conductance calcium-activated channel (subfamily M, alpha member 1); potassium voltage gated channel (Shab-related subfamily, member 2); potassium channel subunit (Slack); potassium intermediate/small conductance calcium-activated channel (subfamily N, member 1); Sodium channel (voltage-gated, type V, alpha polypeptide); amiloride-sensitive cation channel 2 (neuronal); potassium channel (subfamily K, member 6 (TWIK-2)); cation-chloride cotransporter 6; solute carrier family 21 (organic anion transporter, member 12); amino acid transporter system A2; peptide/histidine transporter; choline transporter; solute carrier family 31 (copper transporters, member 1); solu carrier family 13 (sodium-dependent dicarboxylate transporter); solute carrier family 2 (facilitated glucose transporter, member 13); solute carrier family 12 (potassium-chloride transporter, member 5); Solute carrier family 6 (neurotransmitter transporter, serotonin, memb 4); Solute carrier family 2 A2 (glucose transporter, type 2); carboxypeptidase D; ubiquitin specific protease 2; mast cell protease 1; proprotein convertase subtilisin / kexin, type 7; lamin receptor 1 (67kD, ribosomal protein SA); protein tyrosine phosphatase (non-receptor type 1); calcium-sensing receptor; neural receptor protein-tyrosine kinase; glutamate receptor (metabotropic 4); nuclear receptor subfamily 4 (group A, member 2); Neuropeptide Y5 recept protein tyrosine phosphatase (non-receptor type 5); insulin-like growth factor 1 receptor; Prote tyrosine phosphatase (receptor-type, zeta polypeptide); nuclear receptor subfamily 4 (group A, member 3); glutamate receptor (metabotropic 1); Tumor necrosis factor receptor superfamily (member 1a); insulin receptor; gamma-aminobutyric acid receptor associated protein; protein tyrosine phosphatase; non-receptor type 12; cholinergic receptor (nicotinic, beta polypeptide 1 olfactory receptor (U131); Gamma-aminobutyric acid receptor beta 2; glial cell line derived neurotrophic factor family receptor alpha 1; Glycine receptor beta; glutamate receptor interact protein 2; adenylate cyclase activating polypeptide 1 receptor 1; asialoglycoprotein receptor 2; adenosine A3 receptor; Fibroblast growth factor receptor 1; nuclear receptor binding factor 2; purinergic receptor P2Y (G-protein coupled 1); nuclear receptor subfamily 1 (group H, memb 4); peroxisome proliferator activator receptor(gamma); 5 hydroxytryptamine (serotonin) recep 4; retinoid X receptor gamma; insulin receptor-related receptor; putative N-acetyltransferase Camello 4; lecithin-retinol acyltransferase; Phenylethanolamine N-methyltransferase; fucosyltransferase 2; Sialyltransferase 8 (GT3 alpha 2,8-sialyltransferase) C; UDP-

glucuronosyltransferase; alpha 1,3-fucosyltransferase Fuc-T (similar to mouse Fut4); diacylglycerol O-acyltransferase 1; signal transducer and activator of transcription 3; ISL1 transcription factor (LIM/homeodomain); and oligodendrocyte transcription factor 1. In anoth embodiment, the protein is encoded by a gene selected from the group consisting of CNCG, CACNA2D1, KCNC3, and KCNB2.

In another aspect, the invention provides a method for identifying a therapeutic target f the treatment of a disease that involves a physiological or regulatory pathway, such as aberrant glucose metabolism or lipid metabolism, by comparing RNA or protein levels of at least one component of an isolated mRNP complex in a sample from an individual with a disease associated with altered glucose metabolism or lipid metabolism to RNA or protein levels of th component in a healthy sample. If the levels of the component in the diseased sample are different from the levels of the component in the healthy sample, the component, a nucleic aci that encodes the component, or a protein encoded by the component is a potential therapeutic target for the treatment of the disease.

In another aspect, the invention provides a method for identifying a gene or gene produ involved in a physiological or regulatory pathway in a cell, such as a glucose or lipid metaboli pathway. For example, an mRNP complex containing at least one component that participates a glucose metabolic or lipid metabolic pathway is isolated and at least one additional compone of the isolated mRNP complex is identified. The additional component is also likely involved a glucose or lipid metabolic pathway. In an embodiment, the method includes the step of confirming the activity of the additional component by inhibiting the expression of the additio component in a cell or organism and determining the effect of the inhibition on glucose metabolism or lipid metabolism. Inhibition can be achieved by any number of means, includir for example, inhibiting gene expression of the additional component using an RNAi, an antise RNA, a ribozyme, a PNA, or an antibody.

In another aspect, the invention provides a method for identifying an agent that alters a physiological or regulatory pathway in a cell, such as a glucose metabolism or lipid metabolisı A cell sample is treated with an agent and an mRNP complex having at least one component th participates in a metabolic pathway, for example, a glucose metabolic or lipid metabolic pathway, is isolated from the sample, and the RNA or protein levels of at least one component the isolated mRNP complex are measured and compared to the RNA or protein levels of the component isolated from an untreated control sample. Differential expression of the compone

in the agent-treated sample compared to the untreated control sample is indicative that the ager regulates or participates in glucose metabolism or lipid metabolism. In an embodiment, the agent interacts with or regulates a component of a pathway, such as an insulin production pathway, a lipogenesis pathway, an insulin action pathway, a lipid metabolism pathway, or a glucose metabolism pathway, or any pathway that participates in an aspect of glucose and lipid metabolism. In yet another embodiment, the agent inhibits a pathway. In another embodiment the agent enhances a pathway. In an embodiment, the agent is insulin, a beta-adrenergic agoni insulin-like growth factor-1 (IGF-1), glucagon-like peptide-1 (GLP-1), fatty acid, peroxisome proliferator activated receptor (PPAR) ligands (*e.g.*, thiazolidinediones, fibrates, halogenated fatty acids, and tyrosine derivatives), insulin-like growth factor-2 (IGF-2), an RNAi against an RNA binding protein, an enhancer of RNA binding protein expression, and/or glucose.

In a particular aspect, the invention provides a method for identifying a gene product th regulates glucose metabolism in a cell. The expression in an isolated mRNP complex of at lea one gene product of a pancreatic beta cell sample is measured. The gene product may be an RNA binding protein, an mRNA associated with the RNA binding protein, or an mRNP complex-associated protein. The cell sample, such as a pancreatic beta-cell sample, is then treated with an agent, such as, for example, insulin, glucose, insulin-like growth factor-1 (IGF-1), a β-adrenergic agonist, glucose, glucagon-like peptide-1 (GLP-1), fatty acid, a peroxisome proliferator activated receptor (PPAR) ligand, or insulin-like growth factor 2 (IGF-2). The expression of the gene product is then measured after treatment. A difference in the expressio of the gene product after treatment compared to the expression of the gene product before treatment is indicative that the gene product participates in the regulation of glucose metaboli

In another aspect, the invention provides a method for identifying an agent that regulat insulin production and/or its regulated secretion in a pancreatic beta cell. A pancreatic beta cel sample is treated with a nucleic acid capable of binding to at least one RNA binding protein th is capable of binding to a 3' untranslated region or a 5' untranslated region of a preproinsulin mRNA. The nucleic acid is then separated from the RNA binding protein and the RNA bindin protein is identified. In an embodiment, the RNA binding protein binds to a nucleic acid havin a sequence 5'-gaauaaaaccuuugaaagagcacuac-3', 5'-cccaccacuacccuguccaccccucugcaaug-3', or 5 agccctaagtgaccagctacagtcggaaaccatcagcaagcaggtcattgttccaac-3'.

In another embodiment, the invention provides a method for identifying a component o an mRNP complex by transfecting a cell sample with a nucleic acid that inhibits the expressio

of an RNA binding protein associated with the mRNP complex. Total RNA from the cell sam and from a control sample is then isolated and measured. RNAs that have altered expression i the nucleic acid-transfected sample compared to the control sample are considered members o the mRNP complex that share functional and/or structural characteristics (*e.g.e.g.*, that participate in the same metabolic pathway).

In another aspect, the invention provides an isolated mRNP complex, for example, an mRNP complex, containing polypyrimidine tract binding (PTB) and at least one mRNA associated with the PTB protein.

In another aspect, the invention provides methods for identifying a protein that regulate insulin production and/or its regulated secretion by measuring the expression of an RNA bindi protein, an mRNA associated with the RNA binding protein, and/or an mRNP complex-associated protein in a pancreatic beta cell sample, treating the pancreatic beta cell sample with an agent, such as, insulin, a beta-adrenergic agonist, insulin-like growth factor-1 (IGF-1), glucagon-like peptide 1 (GLP-1), fatty acid, peroxisome proliferator activated receptor (PPAR ligands (*e.g.*, thiazolidinediones, fibrates, halogenated fatty acids, and tyrosine derivatives), insulin-like growth factor-2 (IGF-2), RNAi against an RNA binding protein involved in insulin production or secretion, an enhancer of an RNA binding protein expression and/or glucose, an measuring expression of the levels of RNA binding protein, mRNA, and/or an mRNP complex associated protein after treatment. The difference in the expression of the RNA binding protei an mRNA associated with the RNA binding protein, and/or an mRNP complex-associated protein after treatment compared to expression before treatment is indicative that the RNA binding protein, mRNA, associated with the RNA binding protein, and/or an mRNP complex-associated protein regulates insulin production.

In another aspect, the invention provides methods of identifying gene products co-regulated with an mRNA that participates in the glucose or lipid metabolic pathway, such as, f example, preproinsulin mRNA, by isolating an RNA binding protein or mRNP complex-associated protein that binds to the mRNA known to participate in glucose or lipid metabolism and identifying at least one additional component of the mRNP complex (*e.g.*, mRNA, RNA binding protein, and/or mRNP complex-associated protein).

In another aspect, the invention provides methods for assessing the efficacy of an agent as a therapeutic for treating an individual having a disease associated with altered glucose and/ lipid metabolism. The methods comprise the steps of contacting a sample from an individual

having a disease with an agent, and comparing the level of expression of an RNA binding protein, an mRNA associated with the RNA binding protein, or an mRNP complex-associated protein in the agent-treated sample to the level of expression of the RNA binding protein, the mRNA associated with the RNA binding protein, or the mRNP complex-associated protein in a control sample, wherein a difference in expression is indicative that the agent is a candidate therapeutic capable of treating the disease. The methods of the invention are also used to monitor the efficacy or toxicity of an agent.

In another aspect, the invention provides a method to identify genes affected by the activity of a specific RNA binding protein. RNAi-mediated gene silencing is used to inhibit the expression of a specific RNA binding protein. RNA samples are isolated from control RNAi treated cells or tissues and RNA binding protein-specific RNAi treated cells or tissues and gene that are differentially expressed are identified.

The foregoing and other objects, features and advantages of the present invention will be made more apparent from the following drawings and detailed description of preferred embodiments of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

The objects and features of the invention may be better understood by reference to the drawings described below in which,

Figure 1 is a schematic overview outlining an embodiment of the RIBOTRAP™ assay for the isolation of an RNA binding protein (RBP-X) binding to a biotinylated mRNA of interest using a streptavidin-agarose support.

Figure 2 is a schematic overview of the RNA binding protein identification using one type of RIBOTRAP™ assay and subsequent RAS™ assay for identification of mRNA substrate for the RNA binding protein identified by RIBOTRAP™.

Figure 3 shows the general scheme of Ribonomic Analysis System, RAS™ . RAS™involves the isolation of mRNP complexes based upon specific RNA binding proteins and the identification of RNAs dissociated with the mRNP complex. RAS™ can be performed in at least three ways; A) *In vivo* RAS™ using antibodies against the native endogenous RNA binding protein, B) *In vivo* RAS™ using epitope-tagged RNA binding protein and an antibody

against the epitope, C) *In vitro* RAS™ using purified recombinant RNA binding protein and ce extracts or purified RNA.

Figure 4 is a schematic of using RIBOTRAP™ and RAS™ for polypyrimidine tract binding protein (PTB, or RBP-1). A ribonomic cluster is isolated from cell extracts using antibodies specific for RBP-1. RNA extracted from this cluster is compared to total RNA by global microarray analysis.

Figure 5 is a schematic overview of an embodiment of a target discovery process using RNA binding proteins and mRNP complexes.

Figure 6 is a schematic overview of an exemplary data flow for analyzing and interpreting microarray results from comparative RNA binding protein expression and/or mRN complexes for identifying tissue or disease-specific RNA binding proteins, mRNAs, and genes.

Figure 7 is a Western blot illustrating the *in vitro* RIBOTRAP™, verifying that PTB fr INS-1 cell lysates specifically binds the oligonucleotides encoding a portion the 3'UTR of preproinsulin and not oligonucleotides encoding a control oligonucleotide. In addition, glucos stimulates an acute and transient increase in PTB binding. Lanes 1 and 2: total cell lysate; Lan 3 and 4: control oligonucleotides; Lanes 5 and 6: 5' UTR oligonucleotides; Lanes 7 and 8: 3'UTR oligonucleotides.

Figure 8 illustrates a proposed model of glucose-regulated RNA binding protein bindin to preproinsulin mRNA and regulation of glucose-induced preproinsulin translation by RNA binding proteins. Sp, signal peptides; B, C, A, coding regions for various peptide chains of processed insulin.

Figure 9 is a schematic overview of target discovery in primary adipocytes.

Figure 10 is a list of RNA binding protein genes whose expression is differentially regulated (2-fold or more) during differentiation of human pre-adipocytes to adipocytes. RNA was isolated from lean patients pre-adipocytes and RNA from lean patients differentiated adipocytes.

Figure 11 is a list of RNA binding protein genes that are up-regulated 2-fold or more during differentiation of adipocytes from obese patients.

Figure 12 is a list of RNA binding proteins that are differentially expressed (2-fold or more) in human adipocytes treated with BRL-37433. RNA was isolated from human adipocyt

prepared from lean (non-obese) patients that were either left untreated or with the β-3 adrenergic agonist, BRL-37344 (1 μM).

Figure 13 is a list of RNA binding proteins that are differentially expressed (2-fold or more) in human adipocytes treated with insulin. RNA was isolated from human adipocytes prepared from lean (non-obese) patients that were either left untreated or with insulin (100 nM).

Figure 14 is a list of RNA binding proteins that are differentially regulated by glucose in INS-1 cells.

Figure 15 is a list of RNA binding protein genes differentially expressed in HepG2 cells treated with bezafibrate.

Figure 16 is a list of RNA binding protein genes differentially expressed in HepG2 cells treated with Wyeth 14643.

Figure 17 is a list of RNA binding protein genes differentially expressed in HepG2 cells treated with troglitazone.

Figure 18 is a list of RNA binding protein genes differentially expressed in HepG2 cells treated with MCC-555.

Figure 19 is a list of RNA binding protein genes differentially expressed in HepG2 cells treated with ciglitazone.

Figure 20 is a list of RNA binding protein genes differentially expressed in HepG2 cells treated with 2-bromohexadecanoic acid (2-BHDA).

Figure 21 is a list of RNA binding protein genes differentially expressed in HepG2 cells treated with prostaglandin J2 (PJ2).

Figure 22 is a list of RNA binding protein genes differentially expressed in HepG2 cells treated with perfluorooctanoic acid (PFOA).

Figure 23 is a list of genes identified in an *in vitro* RAS™ analysis of GST-PTB. These genes and their encoded proteins represent candidate therapeutic targets of cellular pathways involved in glucose and lipid metabolism, insulin action, insulin resistance, diabetes and obesity.

Figure 24 shows examples of target validation using RNAi mediated gene silencing followed by an assay to determine glucose-stimulated insulin secretion. Figure 24A shows effec of RNAi mediated gene silencing of PTB on insulin secretion. Figure 24B shows effect of RNA

mediated gene silencing of three ion channels contained within the PTB ribonomic cluster. Figure 24C shows the effect of RNAi mediated gene silencing of IonCh4 or CNCG on insulin secretion.

Figure 25 is a schematic for the regulatory mechanisms of insulin secretion in pancreatic beta cells. Proteins that are shown in bold print are present on the PTB cluster.

Figure 26A shows an immunoblot probed with a PTB monoclonal antibody showing PT binding to a preproinsulin 3'UTR oligonucleotide after cells were grown in various amounts of glucose. Figure 26B is a bar graph depicting the data from Figure 26A.

Figure 27 is a refined list of candidate therapeutic targets obtained from the PTB ribonomic cluster and is organized into druggable target classes.

Figure 28 shows the effect of PTB inhibition by RNAi on the expression of PTB, preproinsulin as well as nine additional genes found within the PTB-cluster: CACNA1s, CACNA2D1, Casr, C1c3, KCNJ6, and Loc245960. As indicated in Figure 28A, there was an 80% reduction in PTB mRNA expression, confirming the action of the PTB specific RNAi. Expression of some of the other genes was also downregulated to varying degrees. Figure 28B shows genes whose expression was up-regulated as a result of PTB knockdown, which includes preproinsulin mRNA, which is up-regulated 3-fold.

DETAILED DESCRIPTION

The invention provides methods for mining and characterizing the cellular ribonome in cells that participate in regulatory pathways, such as, for example, insulin action, insulin production and secretion, glucose metabolism, and lipid metabolism. The resulting ribonomic profile provides a subset of genes, and the mRNAs and proteins they encode, as potential therapeutic targets for altering or regulating those pathways.

Methods of the invention comprise identifying and measuring mRNP complex components. Differentially expressed mRNP complex components are potential therapeutic targets, and are useful for assessing the efficacy or toxicity of potential therapeutics. The invention also provides methods for identifying and characterizing structurally and/or functionally related gene products, and for elucidating features of biological pathways or other cellular functions. The identified mRNP complex components are also useful for diagnosing, monitoring, and assessing the metabolic or disease state of a cell or organism.

Generally, mRNP complex components include, but are not limited to, at least one RNA binding protein, and at least one associated or bound mRNA. The mRNP complex may also include at least one associated or bound protein (*i.e.*, an mRNP complex-associated protein) or other associated or bound molecules (*e.g.*, carbohydrates, lipids, vitamins, *etc.*). A component associates with an mRNP complex if it binds or otherwise attaches to the mRNP complex with Kd of about 10^{-5} to about 10^{-12}. In an embodiment, the component associates with the complex with a Kd of about 10^{-7} to about 10^{-9}. In another embodiment, the component associates with the complex with a Kd of about 10^{-8} to about 10^{-9}.

By isolating an mRNP complex from a cell and, preferably, identifying the components of the mRNP complex and the gene precursors and gene products of those components, a ribonomic profile is generated. The associated or bound RNAs are categorized into subsets based on their association with a particular RNA binding protein, mRNP complex-associated protein, mRNA, or other common structural or functional feature. Ribonomic profiles differ from cell sample to cell sample, depending on a variety of factors including, but not limited to, the species or tissue type of the cell, the developmental stage of the cell, the differentiation state of the cell (*e.g.*, malignant) the pathogenicity of the cell (*e.g.*, if the cell is infected, is expressing a deleterious gene, is lacking a particular gene, is not expressing or is underexpressing a particular gene, or is overexpressing a particular gene), the various conditions or agents affecting the cell (*e.g.*, treatment with a therapeutic, environmental, apoptotic or stress state, and the specific ligands used to isolate the mRNP complexes, as well as other factors known to practitioners in the art. The profile therefore provides a footprint of the gene expression of the cell samples that can be used to identify therapeutic targets and to elucidate components of cellular pathways in normal or disease cells.

Identification and Isolation of mRNP Complexes and RNA Binding Proteins

RNA binding proteins involved in a particular pattern, pathway, or disease state, are identified by a variety of methods in the art. For example, the expression of RNA binding proteins that are differentially expressed between normal and disease samples or normal and agent-treated samples can be assessed using methods such as Northern blot, Quantitative Real Time Polymerase Chain Reaction (QRT-PCR), Western blot, microassay analysis, Serial Analysis of Gene Expression (SAGE), cloning and sequencing, or other methods known to the skilled artisan.

Alternatively, differentially expressed RNA binding proteins can be efficiently identified using either a microarray such as a RIBOCHIP™. A RIBOCHIP™ (MWG Biotech, High Point, NC) is a microarray that is used to assay the expression level for a large number of RNA binding proteins. The RIBOCHIP™ contains 50-mer oligonucleotides representing genes, the protein products of which are reported to have RNA binding properties or to contain RNA binding motifs. These genes include those identified in Figures 10-22, and described in Examples 1-5. Also included on the array are control features (a total of 17) that provide information on specificity, labeling and hybridization efficiency, sensitivity and normalization between experiments.

In an embodiment, cell samples containing mRNAs encoding RNA binding proteins are used to probe a microarray containing nucleic acid sequences encoding at least a portion of a number of RNA binding proteins, in order to detect and/or measure the expression of RNA binding proteins in the sample. Sample mRNAs are prepared from cell lines or tissues from control, agent-treated, normal, or diseased states, for example. The agent may be any agent that alters gene expression, for example, glucose, insulin, a beta-adrenergic agonist (*e.g.*, BRL-37433), insulin-like growth factor-1 (IGF-1), glucagon-like peptide-1 (GLP-1), fatty acid, peroxisome proliferator activated receptor (PPAR) ligands (*e.g.*, thiazolidinediones, fibrates, halogenated fatty acids, and tyrosine derivatives), insulin-like growth factor-2 (IGF-2). The agent may also be an RNAi that inhibits an RNA binding protein, an enhancer of RNA binding protein expression, a nucleic acid, a hormone, an antibody, an antibody fragment, an antigen, a cytokine, a growth factor, a pharmacological agent (*e.g.*, chemotherapeutic, carcinogenic), a chemical composition, a protein, a peptide, and/or a small molecule. The mRNA samples are amplified if necessary, and processed for microarray hybridization.

Microarray analysis enables RNA binding protein genes with unique or differential expression profiles to be quickly identified and clustered into functional or structural categories from among the thousand genes profiled in a single experiment. Several specific examples of microarray analysis and lists of relevant RNA binding protein genes and encoded proteins that are differentially expressed are provided in Examples 3-5. These differentially expressed RNA binding proteins genes are involved in, for example, obesity, adipocyte differentiation, insulin action, insulin production and secretion, diabetes, mechanisms of action of PPAR ligands, insulin resistance, glucose metabolism, lipid

metabolism, hypoglycemia, glucotoxicity, lipid toxicity, insulin resistance, hyperlipidemia, and lipodystrophy.

Pancreatic beta cell lines or freshly prepared islets are physiologically relevant *ex vivo* model systems for examining glucose-responsiveness and endocrine pancreas functions. To identify RNA binding proteins that undergo changes in expression, cells are incubated under conditions of low (*e.g.*, 3 mM) or high (*e.g.*, 15 mM) glucose for various periods of time. Total mRNA is prepared according to standard methods. In some cases where samples are limiting, it may be necessary to amplify the mRNA according to standard RT-PCR methods or kits such as the RIBOAMP™ kit (Arcturus, Mountain View, CA). Differentially expressed RNA binding protein genes identified by microarray analysis represent RNA binding proteins whose expression is regulated by glucose.

In another embodiment, mRNA and protein levels of RNA binding proteins are determined in cell lines such as the alpha cell line, α-TC1.6, the rat pancreatic beta cell line INS 1 cells (Beta-gene, Dallas, TX), and mouse pancreatic beta cell line MIN-6 cells, for example, t characterize the mechanisms of gene expression that are particular to that cell type. For example, α-TC1.6 cells express Nkx6.1 mRNA but do not express Nkx6.1 protein. In contrast, INS-1 cells express both Nkx6.1 mRNA and Nkx6.1 protein. Current evidence supports a role for RNA binding proteins in this restrictive expression during islet development.

In another embodiment, human preadipocytes or adipocytes are isolated from lean or obese patients and differential expression of RNA binding proteins is obtained by microarray analysis. These RNA binding protein genes and their gene products function in adipocyte differentiation, adipocyte function, insulin action, insulin resistance, obesity and glucose and lipid metabolic pathways, for example.

RIBOTRAP™

Whereas microarray analysis allows for the simultaneous analysis of the expression of RNA binding proteins, RIBOTRAP™ combines a biochemical and molecular biological approach for isolating, or "trapping", an unknown RNA binding protein or set of RNA binding proteins that interact with an nucleic acid of interest. This involves several different approaches, including the use of 1) affinity-labeled or epitope-tagged RNA binding elements as affinity reagents for *in vitro* isolation of RNA binding proteins and 2) expression or transformation of an affinity-labeled or epitope-tagged mRNA in cell culture models for

isolation of RNA binding proteins bound to the tagged mRNA *in vivo*. RIBOTRAP™ is useful when it is necessary to first identify an RNA binding protein on a specific mRNA. RIBOTRAP™ methods are described in detail in Example 2.

Figure 1 illustrates an example of an *in vitro* RIBOTRAP™ method in which a biotinylated mRNA attached to a streptavidin-agarose support is used to identify and isolate an RNA binding protein present in a cell extract, according to standard methods.

Figure 2 illustrates one embodiment of the invention, in which an mRNA or portion of a mRNA of interest, "RNA Y", is used as "bait" to trap a new RNA binding protein (hexagon). Preferably, RNA Y is first converted to a cDNA using standard molecular biology techniques and is subsequently ligated at the 3' or 5' end to a DNA tag (dotted lines) that encodes a sequenc that will bind a ligand (Protein "X"). The resulting fusion RNA is expressed in cells, where endogenous RNA binding proteins can bind and interact with RNA Y. The cells are then lysed and cell-free extracts are prepared and contacted with Protein X, which has been immobilized o a solid support. After incubation, Protein X and the attached RNA fusion molecule and its associated RNA binding proteins are washed to remove residual cellular material. After washing, the newly isolated RNA binding proteins are removed from the RNA-protein complex and identified by protein microsequencing or Western blotting. Useful ligands include mRNP complex-specific antibodies or proteins (*e.g.*, obtained from a subject with an autoimmune disorder or cancer). The RNA binding protein is further tested for its ability to regulate the translation of the protein encoded by RNAY, and is tested for validation as a drug target.

In an embodiment, an RNA binding protein is isolated by RIBOTRAP™ from a natural biological sample such as an islet, a pancreatic beta cell, an adipocyte, a preadipocyte, a skeletal muscle cell, a cardiac muscle cell, a hepatocyte, or a population of cells. The population of cells may contain a single cell type. Alternatively, the population of cells may contain a mixture of different cell types from either primary or secondary cultures or from a complex tissue, such as an islet or tumor.

In one embodiment, the RNA binding protein is isolated from a cell sample in which the expression of a component of an mRNP complex, or precursor thereof, has been altered, *e.g.*, induced, inhibited, or over-expressed, *e.g.*, by introduction into the sample or other genetic alteration or after treating the cell or tissue with an agent such as glucose, insulin, a beta-adrenergic agonist, insulin-like growth factor-1 (IGF-1), glucagon-like peptide-1 (GLP-1), fatty acid, peroxisome proliferator activated receptor (PPAR) ligands (*e.g.*

thiazolidinediones, fibrates, halogenated fatty acids, and tyrosine derivatives), insulin-like growth factor-2 (IGF-2), an RNAi against an RNA binding protein, an enhancer of RNA binding protein expression, a nucleic acid, a hormone, an antibody, an antibody fragment, an antigen, a cytokine, a growth factor, a pharmacological agent (*e.g.*, chemotherapeutic, carcinogenic), a chemical composition, a protein, a peptide, and/or a small molecule. Where the compound is a nucleic acid, the nucleic acid may be a DNA, RNA, a PNA, an antisense nucleic acid, a ribozyme, an RNAi, an miRNA, an ncRNA, an rRNA, an siRNA, an snRNA, an snoRNA, an stRNA, a tRNA, an aptamer, a decoy nucleic acid, or a competitor nucleic acid, for example. In one embodiment, the compound may alter the expression of an mRNP complex component through competitive binding. A compound may inhibit binding between two or more mRNP complex components, such as between an RNA binding protein and an RNA, between an RNA binding protein and an mRNP complex-associated protein, between an RNA and an mRNP complex-associated protein, or between two RNAs, RBPs, or mRNP complex-associated proteins, for example. In another embodiment, the cell sample is infected with a pathogen, such as a virus, bacteria, prion, fungus, parasite, or yeast, for example, to alter expression of one or more mRNP complex components. Introduction of a nucleic acid encoding one or more mRNP complex components may be achieved by infection, transformation, or other similar methods known in the art. In one embodiment, an expression vector expressing one or more components of an mRNP complex is transfected into a cell. Suitable vectors include, but are not limited to, recombinant vectors such as plasmid vectors or viral vectors. The nucleic acid encoding the component is preferably operatively linked to appropriate promoter and/or enhancer sequences for expression in the cell. In an embodiment of the invention, a specific cell type is engineered to contain a cell type-specific or inducible gene promoter that drives expression of an RNA binding protein.

Alternatively, a knock-out cell line or knock-out organism may be produced, which either does not express a component of an mRNP complex or expresses decreased levels of the component. Preferably, the knock-out cell line or knock-out organism does not express a particular RNA binding protein, mRNA, and/or mRNP complex-associated protein associated with the mRNP complex.

In a preferred embodiment, the nucleic acid encoding the mRNP complex component is tagged in order to facilitate the separation, and/or detection, and/or measurement of the components. Accessible epitopes may be used or, where the epitopes on the components are

inaccessible or obscured, epitope tags on ectopically expressed recombinant proteins may be used. Suitable tags include, but are not limited to, biotin, the MS2 protein binding site sequence the U1snRNA 70k binding site sequence, the U1snRNA A binding site sequence, the g10 binding site sequence (Novagen, Inc., Madison, WI), and FLAG-TAG® (Sigma Chemical, St. Louis, MO). For example, a cell is transfected with a vector directing the expression of a tagged RNA binding protein and a ligand, such as an antibody or antibody fragment, that is specific for the tag, is used to immunoprecipitate the tagged RNA binding protein with its associated mRNAs from a tissue extract containing the transformed cell.

The expression of one or more mRNP complex components may be altered by contacting or treating the cell sample with a known or test compound. The compound may be, but is not limited to, a protein, a nucleic acid, a peptide, an antibody, an antibody fragment, a small molecule, an enzyme, or agents such as glucose, insulin, a beta-adrenergic agonist, insulin-like growth factor-1 (IGF-1), glucagon-like peptide-1 (GLP-1), fatty acid, peroxisome proliferator activated receptor (PPAR) ligands (*e.g.* thiazolidinediones, fibrates, halogenated fatty acids, and tyrosine derivatives), insulin-like growth factor-2 (IGF-2), RNAi against a RNA binding protein an enhancer of RNA binding protein expression, and/or a small molecule (*e.g.*, a putative drug).

RAS™

Once partial sequence of the RNA binding protein is obtained, the corresponding gene may be identified from known databases of cDNA and genomic sequences or isolated from a cDNA or genomic library and sequenced according to art known methods. Preferably, the gene is isolated, the protein is expressed.

Once an RNA binding protein of interest is identified, an antibody is generated against the recombinant RNA binding protein using known techniques. The antibodies are then used to recover and confirm the identity of the endogenous RNA binding protein. Subsequently, the antibody can be used for the Ribonomic Analysis System (RAS™) whereby the mRNP complex containing the RNA binding protein is isolated and the subset of cellular RNAs that are associated with the mRNP complex and RNA binding protein are identified by microarray analysis, which is illustrated in Figure 3 and described in more detail below.

While any method for the isolation of an mRNP complex or its components may be used in the present invention, the methods described herein or in U.S. Patent No. 6,635,422 or disclosed in co-pending U.S. Application Nos. 10/238,306 and 10/309,788 are preferred. For

example, *in vivo* methods for isolating an mRNP complex involve contacting a biological sampl that includes at least one mRNP complex with a ligand that specifically binds a component of th mRNP complex, such as an RNA binding protein. For example, the ligand may be an antibody, a nucleic acid, or any other compound or molecule that specifically binds the component of the complex.

In another embodiment, the mRNP complex is separated by binding the ligand (now bound to the mRNP complex) to a binding molecule that specifically binds the ligand. The binding molecule may bind the ligand directly (*e.g.*, a binding partner specific for the ligand), or may bind the ligand indirectly (*e.g.*, a binding partner specific for a tag on the ligand). Suitable binding molecules include, but are not limited to, protein A, protein G, and streptavidin. Bindin molecules may also be obtained by using the serum of a subject suffering from a disorder such a an autoimmune disorder or cancer. In an embodiment, the ligand is an antibody that binds a component of the mRNP complex via its Fab region and a binding molecule binds the Fc region of the antibody.

In another embodiment, the binding molecule is attached to a solid support such as a bead, well, pin, plate, or column. Accordingly, the mRNP complex is attached to the support vi the ligand and binding molecule. The mRNP complex may then be collected by removing it from the support (*e.g.*, by washing or eluting it from the support using suitable solvents and conditions that are known to a skilled artisan).

In certain embodiments, the mRNP complex is stabilized by cross-linking prior to binding the ligand thereto. Generally, cross-linking involves covalent binding (*e.g.*, covalently binding the components of the mRNP complex together). Cross-linking may be carried out by physical means (*e.g.*, by heat or ultraviolet radiation), or chemical means (*e.g.*, by contacting the complex with formaldehyde, paraformaldehyde, or other known cross-linking agents), methods of which are known to those skilled in the art. In another embodiment, the ligand is cross-linkec to the mRNP complex after binding to the mRNP complex. In additional embodiments, the binding molecule is cross-linked to the ligand after binding to the ligand. In yet another embodiment, the binding molecule is cross-linked to the support.

The methods of the invention allow for the isolation and characterization of a plurality o mRNP complexes simultaneously (*e.g.*, "*en masse*"). For example, a biological sample is contacted with a plurality of ligands each specific for different mRNP complexes. A plurality o mRNP complexes from the sample bind the appropriate specific ligands. The plurality of mRNI

complexes are then separated using appropriate binding molecules, thereby isolating the plurali of mRNP complexes. The mRNP complexes and the mRNAs contained within the mRNP complexes are then characterized and/or identified by methods described herein and known in the art. Alternatively, the methods of the invention are carried out on a sample numerous times and the mRNP complexes are characterized and identified in a sequential fashion, with each iteration utilizing a different ligand.

Following isolation of an mRNP complex, the level of expression of at least one mRNA associated with the mRNP complex is determined. The collection of mRNAs, together with the RNA binding proteins, and mRNP complex-associated proteins on a particular mRNP complex provides a ribonomic profile, that is indicative of the gene expression of a subset of functionally related gene products. It will be appreciated that ribonomic profiles differ from cell to cell as described previously. Thus, a ribonomic profile for one cell type can be used as an identifier fo that cell type and can be compared with ribonomic profiles of other cells.

Figure 4 illustrates an embodiment of the invention in which the RAS™ technology is used in conjunction with a RIBOTRAP™ method to identify functionally and/or structurally related mRNAs associated with an mRNP complex. Figure 4 shows a comparison of the data obtained using traditional analysis of total RNA compared to the data obtained using RIBOTRAP™ to first isolate a particular RNA binding protein is followed by the use of RAS™ to identify associated mRNAs. The use of RIBOTRAP™ and RAS™ provides a more sensitiv assay that is enriched for the subset of RNAs associated with a particular RNA binding protein and which are likely functionally related. By comparison, microarray analysis of total RNA do not provide the same level of sensitivity and functionality and provides a more complex data se

Amplification of the mRNA isolated according to the methods of the invention and/or th cDNA obtained from the mRNA is not necessary or required by the present invention. Howeve the skilled artisan may choose to amplify the nucleic acid that is identified according to any of the numerous nucleic acid amplification methods that are well-known in the art (*e.g.*, polymera chain reaction (PCR), reverse transcriptase polymerase chain reaction (RT-PCR), quantitative real time polymerase chain reaction (QRT-PCR), rolling circle amplification (RCA), or strand displacement analysis (SDA)).

One goal of the RAS™ assay is to identify mRNAs that encode proteins that have functional relationships. Among the related functions that are expected are a) involvement of encoded proteins in a common metabolic pathway, b) encoded proteins that are temporally co-

regulated, c) encoded proteins that are similarly localized in or on the cell, d) encoded proteins that play a role in forming or regulating a biological machine (*e.g.*, a ribosome). The identification of complex traits and phenotypes that result from the expression of a set of functionally-related proteins would include such processes as cognition, cell-specific activation, inflammation, or differentiation. While proteins known to be involved in these complex processes are known from other studies, the majority of the functions remain largely unknown. One of the values of the invention is for discovering a larger set of proteins involved in these processes that could serve as alternative drug targets or surrogate markers.

In addition, the subpopulation of mRNAs that are present in an mRNP complex can be identified and examined for the presence of common sequence elements, such as 5' or 3' untranslated regions, or common functional features. RAS™ can then be used to identify the unique subsets of RNAs associated with those RNA binding proteins. Computational analysis o the primary sequence for identifying Untranslated Sequence Elements for Regulation Codes (USER codes) may be used alone or in combination with secondary structure analysis. In addition, the subpopulation of mRNAs can be examined for functional relationships. For example, each mRNA can be categorized by gene annotation and by known functions in functional genomics databases (*e.g.*, Locus Link (NCBI, Bethesda, MD), GO Database (Gene Ontology™ Consortium), Proteome BioKnowledge® Library (Incyte Genomics, Inc., Palo Alto CA)). For example, if the RNA binding protein or mRNP complex is involved in immune regulation, the other mRNAs found in the same mRNP complex can be analyzed for their role in immune regulation. However, the mRNA could be bound indirectly through a different RNA binding protein or RNA in the mRNP complex (*e.g.*, is assessed for the presence of the USER code element in its UTR that recognizes the RNA binding protein or other known binding sites for RNA binding proteins).

An exemplary technique for isolating functional clusters of mRNAs is *in vivo* RAS™, whereby the unique repertoire of mRNAs (defined herein as a "functional cluster") that is associated with a particular RNA binding protein *in vivo* is identified. Alternatively, *in vitro* RAS™ may be used, wherein the RNA binding proteins and mRNAs are associated *in vitro* and analyzed. The *in vitro* technique is useful if, for example, the RIBOTRAP™ technique for isolating endogenous RNA:protein complexes is not feasible, for example due to ineffective affinity reagents for immunoprecipitation of the intact endogenous complex.

In vitro RAS™

Example 5 provides examples of methods for performing *in vitro* RAS™. Briefly, an RNA binding protein is cloned by polymerase chain reaction (PCR) and the sequence verified and expressed in *E. coli* as a glutathione S transferase (GST) fusion protein. Following purification, the GST-RNA binding protein was attached to glutathione Sepharose beads and exposed to mRNA preparations to assess its ability to selectively retain discreet mRNA pools. Messenger RNA retained by an individual GST-RNA binding protein was profiled by combined microarray and QRT-PCR analyses, according to standard methods. Messenger RNA untranslated region (UTR) sequences are aligned to search for obvious consensus elements in the retained mRNA pools, and a small number (*e.g.*, 5-10 UTRs) are initially evaluated to confirm direct binding by biotinylated oligonucleotide-affinity chromatography (as described for RIBOTRAP™).

In general, two types of mRNA preparations are used, purified cytoplasmic RNA and cleared cytoplasmic lysates. Purified cytoplasmic RNA is used to directly identify mRNAs that encode *cis* binding elements for the RNA binding protein. Cellular lysates containing both RNA and protein may have improved specificity of the RNA binding protein:RNA interaction, for example, due to the presence of auxiliary factors that modulate binding.

For additional glucose and/or lipid-regulated RNA binding proteins, comparisons are made between mRNA pools retained using purified RNA or cytoplasmic lysates (as described for RAS™) prepared from cells or tissue treated with an agent such as glucose, insulin, a beta-adrenergic agonist, insulin-like growth factor-1 (IGF-1), glucagon-like peptide-1 (GLP-1), fatty acid, peroxisome proliferator activated receptor (PPAR) ligands (*e.g.* thiazolidinediones, fibrates, halogenated fatty acids, and tyrosine derivatives), insulin-like growth factor-2 (IGF-2), RNAi against a RNA binding protein, an enhancer of RNA binding protein expression, and/or a small molecule (*i.e.*, a putative drug).

Example 6 describes an example of *in vitro* RAS™. In short, human PTB was cloned into a glutathione S transferase vector and recombinant protein (GST-PTB) was purified as known to those skilled in the art. GST-PTB was immobilized onto glutathione Sepharose beads and incubated with cleared cytoplasmic lysates or purified RNA prepared from pancreatic beta cells. The matrix is washed thoroughly with binding buffer and RNAs bound to GST-PTB were purified. As a control, the same RNA preparations were incubated with a

glutathione bound matrix containing GST protein alone or another GST-RNA binding protein. The purified RNA from each column was identified by microarray analysis or QRT-PCR.

In vivo RAS™

In another embodiment of the invention, endogenous mRNP complexes from cells or tissue are profiled by immunoprecipitation of endogenous mRNP complexes from cell lysates and characterization of mRNA content. A binding partner (*e.g.*, an antibody) to an individual RNA binding protein or other mRNP complex component is used to isolate the mRNP complex and identify and characterize the associated mRNAs, *e.g.*, during any given disease state or under certain experimental conditions. In contrast to the tagged RNA binding protein approach described for *in vitro* RAS™ isolation of endogenous RNA binding protein complexes does not require transfection and selection of cell lines expressing tagged RNA binding proteins prior to analysis. However, *in vivo* RAS™ analysis requires antibodies specific for individual RNA binding proteins or other mRNP complex component that can immunoprecipitate intact endogenous mRNP complexes. Polyclonal anti-peptide and\or full-length protein antibodies, monoclonal antibodies, or recombinant antibody libraries specific for a mRNP complex component such as an RNA binding protein may be used. For example, a commercial antibody for the RNA binding protein PTB (Zymed, South San Francisco, CA) was used to effectively immunoprecipitate PTB-containing mRNP complexes from INS-1 cells.

Antibodies and fragments thereof that bind to mRNP complexes are generated using methods that are well known in the art. Such antibodies may include, but are not limited to, polyclonal, monoclonal, chimeric, single chain, Fab fragments, and fragments produced by a Fal expression library. Antibodies and fragments thereof may also be generated using antibody phage expression display techniques, which are known in the art.

For the production of antibodies, various hosts including, but not limited to, goats, pigs, rabbits, rats, chickens, mice, and humans are immunized by injection with the mRNP complex o any fragment or component thereof that has immunogenic properties. Depending on the host species, an adjuvant is used to increase the immunological response. Such adjuvants include, bu are not limited to, Freund's, mineral gels such as aluminum hydroxide, and surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, keyhole

limpet hemocyanin, and dinitrophenol. Among adjuvants used in humans, Bacilli Calmette-Guerin and Corynebacterium parvum are preferable.

Monoclonal antibodies to the components of the mRNP complex are prepared using any technique that provides for the production of antibody molecules by a cultured cell line. These include, but are not limited to, the hybridoma technique, the human B-cell hybridoma technique, and the EBV-hybridoma technique. Generally, an animal is immunized with the mRNP complex or immunogenic fragment(s) or conjugate(s) thereof. Lymphoid cells (*e.g.*, splenic lymphocytes) are then obtained from the immunized animal and fused with immortalized cells (*e.g.*, myeloma or heteromyeloma) to produce hybrid cells. The hybrid cells are screened to identify those that produce the desired antibody.

Antibodies may also be produced by inducing *in vivo* production in the lymphocyte population or by screening immunoglobulin libraries or panels of highly specific binding reagents as is known in the art.

Antibody fragments that contain specific binding sites for mRNP complexes may also be generated. For example, such fragments include, but are not limited to, the $F(ab')_2$ fragments that can be produced by pepsin digestion of the antibody molecule and the Fab fragments that can be generated by reducing the disulfide bridges of the $F(ab')_2$ fragments. Alternatively, Fab expression libraries are constructed to allow rapid and easy identification of monoclonal Fab fragments with the desired specificity.

Various immunoassays are used to identify antibodies having the desired specificity for the mRNP complex. Numerous protocols for competitive binding or immunoradiometric assays using either polyclonal or monoclonal antibodies with established specificities are well known in the art. Such immunoassays typically involve the measurement of complex formation between the component of the mRNP complex and its specific antibody. An immunoassay utilizing monoclonal antibodies reactive to two non-interfering epitopes is preferred, but a competitive binding assay may also be employed.

The antibodies may be conjugated to a support suitable for a diagnostic assay (*e.g.*, a solid support such as beads, plates, slides or wells formed from materials such as latex or polystyrene) in accordance with known techniques. Antibodies may likewise be conjugated to detectable groups such as radiolabels (*e.g.*, ^{35}S, ^{125}I, ^{131}I), enzyme labels (*e.g.*, horseradish peroxidase, alkaline phosphatase), and fluorescent labels (*e.g.*, fluorescein) in accordance with

known techniques. Such devices preferably include at least one reagent specific for detecting th binding between an antibody and the RNA binding protein. The reagents may also include ancillary agents such as buffering agents and protein stabilizing agents (*e.g.*, polysaccharides an the like). The device may further include, where necessary, agents for reducing background interference in a test, control reagents, apparatus for conducting a test, and the like. The device may be packaged in any suitable manner, typically with all elements in a single container, along with a sheet of printed instructions for carrying out the test.

In an embodiment, full-length RNA binding protein genes are amplified by PCR from appropriate cDNA libraries and cloned into expression vectors (*e.g.*, pGEX or pDEST17 6X-His) for bacterial expression, purification, and antibody production. Antibodies are affinity-purified, characterized, and optimized for immunoprecipitation of the protein and its associated RNA binding proteins or mRNP complex. The ability of the antibody to precipitate RNAs in general is determined by a rapid, high-throughput analysis using a 2100 BioAnalyzer (Agilent, Palo Alto, CA). Non-immune controls include previously characterized RNA binding protein antibodies are run in parallel as negative and positive controls, respectively. Specific antisera that are able to immunoprecipitate the RNA binding protein and/or mRNP complex are used for further analysis.

Optionally, more than one peptide antigen may be chosen based on analysis of the protein sequence using software for antigenic determination (Antheprot, Lyon, France; uses Parker and Wellington algorithms), followed by a Blast P search in NCBI to ensure that the designed peptide is not significantly homologous to another protein. Peptides are selected from regions thought to lie outside the RNA binding domain, to enrich for epitopes that are more likely to be exposed in the mRNP complex. In an embodiment, 15-25 amino acid peptides are synthesized according to standard methods and conjugation to Keyhole limpet hemocyanin (KLH), followed by immunization of rabbits for polyclonal antibody production.

RNA binding proteins or mRNP complexes may be immunoprecipitated as follows. In an embodiment, antibodies specific for a particular RNA binding protein /mRNP complex are pre-bound to protein A beads, blocked with bovine serum albumin and washed extensively. After a final wash in lysis buffer, cell extracts are added. Nuclei-free cytosolic extracts are prepared essentially as described from cells (or tissue) that have been exposed to various experimental conditions (*e.g.*, low and high glucose). Incubation times and

temperatures are optimized for each anti-RNA binding protein antibody. The complexes are washed under nuclease-free conditions. The antibody-mRNP complex is then disrupted with denaturing buffer RLT (Qiagen, Inc., Valencia, CA), containing guanidine thiocyanate, and mRNA purified using Qiagen RNA isolation column chromatography (Qiagen, Inc., Valencia, CA). The purified mRNA is then processed for microarray analysis, for example on human or rodent microarrays (depending on the cell or tissue source) comprised of features (*e.g.*, 10,000-40,000 genes) representing up-to-date genomic content (*e.g.*, Affymetrix, Santa Clara, CA; Agilent, Palo Alto, CA or MWG Biotech, Inc. High Point, NC). A gene observed at 'detectable' levels that is present in each of the experiments is considered a component of mRNP complex to which it is associated and its relative fold-enrichment above a total RNA microarray analysis is determined. Routinely, genes expressed at a level above local background are considered members of that cluster. The presence of the candidate genes and their relative fold-enrichment over total RNA are verified and more accurately quantified by QRT-PCR using sequence-specific primers.

In an embodiment, the combination of the *in vitro* and *in vivo* RAS™ based approaches may be used to map mRNP complex pools and accurately define the RNA content of selected mRNP complexes.

The multicomponent nature of mRNP complexes can interfere with efficient immunoprecipitation due to inaccessibility of reactive polypeptide epitopes. In the absence of appropriate affinity reagents or when endogenous complexes cannot be isolated, mRNAs associated with individual RNA binding proteins in a cell are identified by using RNA binding proteins tagged with one of several generic epitopes such as, for example, Flag, AU1, or T7. The binding epitopes are expressed on the N- or C-terminus of the RNA binding protein and introduced into an appropriate cell line for expression. Pooled cell lines are generated by selection (*e.g.*, in zeocin) and screened for stable expression of the tagged RNA binding proteins Commercially available antibodies (*e.g.*, α-T7, Novagen, Madison, WI) are used to immunoprecipitate mRNP complexes from cells, for example, INS-1 cells following mock or glucose treatment. As a positive control, tagged poly A binding protein (PABP1), which is known to bind virtually all polyadenylated mRNAs, is constructed and transfected into INS-1 cells for parallel immunoprecipitation of mRNP complexes. Messenger RNA pools isolated following low and high glucose treatment of the individual INS-1 cell lines (pooled lines) are evaluated by microarray analysis and selective QRT-PCR confirmation. The use of a tagged-

RNA binding protein is advantageous in that the functional cluster associated with the tagged-RNA binding protein can be directly compared with that isolated using a commercially available monoclonal antibody to the RNA binding protein. This allows for validation of the endogenous RNA binding protein cluster as well as assessment of the mRNA binding characteristics of the tagged-RNA binding protein.

The mRNA pools were converted into amino allyl cDNAs and labeled with cyanine dyes for use as probes on microarrays. Aminoallyl cDNA (aa-cDNA) was synthesized from RNA preps based on modifications of protocols by DeRisi (www.microarray.org; "Reverse Transcription and aa-UTP Labeling of RNA") and TIGR (www.tigr.org; Protocol M005), as described in Example 1. Purified aa-cDNA was coupled to cyanine dyes (Amersham Biosciences; Piscataway, NJ; Catalog # PA23001 (Cy3) or PA25001 (Cy5)), purified, and analyzed as described in Example 1.

For each microarray, material from one Cy3 labeling and one Cy5 labeling reaction were pooled and dried in a speed vac. The pooled samples were then hybridized to the microarray and the slides processed according to the general guidelines suggested by the manufacturer (MWG Biotech; High Point, NC).

Microarrays were scanned using an Axon 4000B Scanner and GenePix version 4.0 software (Axon; Union City, CA) and the resulting image files were quantified as described in Example 1.

An isolated mRNP complex can be examined, in part to determine expression of its components as a whole, or broken down into its individual components. The mRNP complex can be separated from the ligand as a whole, or the mRNA can be separated from the ligand-mRNP complex, followed by separation of the RNA binding protein from the ligand. Alternatively, if the mRNA is bound to the ligand, the RNA binding protein can be separated from the ligand-mRNA complex, and the mRNA then separated from the ligand. Practitioners in the art are aware of standard methods of separating the components, including washing and chemical reactions. After separation, each component of an mRNP complex can be examined and their identity, quantity, or other identifying factors preferably recorded (*e.g.*, in a computer database) for future reference.

cDNAs or oligonucleotides can be used to identify complementary mRNAs on mRNP complexes partitioned according to methods disclosed herein. cDNA or oligonucleotide based

microarray grids can be used to identify mRNA subsets *en masse*. Each target nucleic acid examined on a microarray has a precise address that can be located, and the binding can be quantitated. Microarrays may be arranged in a commercially available substrate (*e.g.*, paper, nitrocellulose, nylon, any other type of membrane filter, chip, such as a siliconized chip, glass slide, silicone wafer, or any other suitable solid or flexible support). In addition, mRNAs in a sample can be identified based upon the stringency of binding and washing, a process known as "sequencing by hybridization", according to standard methods.

Alternative approaches for identifying, sequencing and/or otherwise characterizing the mRNAs in an mRNA subset include, but are not limited to, differential display, phage display/analysis, Serial Analysis of Gene Expression (SAGE), and preparation of cDNA libraries from the mRNA preparation and sequencing of the members of the library.

Methods for DNA sequencing that are well known and generally available in the art may be used to practice any of the embodiments of the invention. The sequencing methods may employ such enzymes as the Klenow fragment of DNA polymerase I, SEQUENASE® (U.S. Biochemical Corp, Cleveland, OH), Taq polymerase (Perkin Elmer, Boston, MA), thermostable T7 polymerase (Amersham, Chicago, IL), or combinations of polymerases and proofreading exonucleases such as those found in the Elongase® Amplification System marketed by Gibco BRL (Invitrogen™, Carlsbad, CA). Preferably, the process is automated with machines such as the Hamilton Micro Lab 2200 (Hamilton, Reno, NV), Peltier Thermal Cycler (PTC200) (MJ Research, Watertown, MA) and the ABI Catalyst and 373 and 377 DNA Sequencers (Perkin Elmer, Shelton, CT).

In an embodiment, the methods of the invention are carried out on isolated nuclei from cells that are undergoing developmental or cell cycle changes or that have otherwise been subjected to a cellular or an environmental change, performing nuclear run-off assays according to known techniques to obtain transcribing mRNAs, and comparing the transcribing mRNAs with the global mRNA levels isolated from mRNP complexes from the same cells using cDNA microarrays. These methods can distinguish transcriptional from post-transcriptional effects on steady state mRNA levels *en masse*. As opposed to a total RNA or a transcription profile that depicts RNA accumulation representing a steady-state level of mRNA, which is affected by transcriptional and post-transcriptional events, the mRNAs detected by nuclear run-off experiments represent only the transcription of a gene before the influence of post-transcriptional

events. The microarrays representing mRNP complexes contain discrete and more limited subsets of mRNAs than the transcriptome or nuclear run-offs.

Other methods for characterizing and identifying mRNP complex components include standard laboratory techniques such as, but not limited to, RT-PCR, QRT-PCR, RNAse protection, Northern Blot analysis, Western blot analysis, macro- or micro-array analysis, *in situ* hybridization, immunofluorescence, radioimmunoassay, and immunoprecipitation. The results obtained from these methods are compared and contrasted in order to characterize further the functional relationships of the mRNA subsets and other mRNP components.

The present invention also provides diagnostic methods for assessing the cell types present in a sample or a population of cells such as pancreatic beta cells, adipocytes, preadipocytes, hepatocytes, skeletal muscle, and cardiac muscle. Such analyses can distinguish one cell type from another, cell types of different differentiation states, or cells from one person from another person, for example, a person with a disease or increased risk of disease, from a normal person. The method involves isolating at least one mRNP complex and detecting the expression of at least one component of the mRNP complex, wherein the at least one component is specific for a certain cell type, so that the detection of the expression of the component is indicative of the presence of the cell type in the population of cells. The component may be specific for a certain cell type within an entire sample (*e.g.*, tissue or organism) or within the population of cells. The sample or population of cells may be, for example, a tumor, a tissue, a cultured cell, a body fluid, an organ, a cell extract or a cell lysate. The methods of the invention may also be used to determine the cell types present in a population of cells. Alternatively, cell type, as used herein, may also refer to a class of cells derived from a particular tissue, a particular species, a particular state of differentiation, a particular disease state, or a particular cell cycle.

Validation of Functional Role for Genes Encoding Components of mRNP Complexes

To confirm that a component identified in the an mRNP complex plays a direct role in the etiology of a disease or other phenotype, candidate target genes encoding that component are chosen for gene silencing studies (*e.g.*, using antisense nucleic acids, RNAi, ribozymes, and/or transgenic animals). Comparison of RNA from control RNAi-treated samples with RNA prepared from RNA binding protein RNAi-treated samples can provide quantitative differences in gene expression. Differential expression of genes in samples isolated from RNA binding protein-specific RNAi-treated cells or tissues provides data on identification and quantitative

changes in expression due to inhibition of the specific RNA binding protein by RNAi. Genes whose expression patterns are altered as a result of down-regulation of the specific RNA binding protein would be tentatively considered as a member of that RNA binding protein ribonomic cluster.

For example, for each candidate therapeutic gene, one or more short DNA segments representing the coding sequence of that gene is individually cloned into a plasmid vector in the sense or antisense direction, downstream of an appropriate promoter, such as a U6 polymerase III promoter or RNAse P RNA H1. Plasmid vectors may be constructed that contain two or more short DNA segments of one or more candidate therapeutic genes in the sense and antisense directions, downstream of a U6 polymerase III promoter or RNAse P RNA H1. Alternatively, one may construct an RNAi by annealing chemically synthesized complementary 22 bp RNAs (Dharmacon, Lafayette, CO).

Following transfection of the vector or double stranded RNA into cultured cells according to standard methods, phenotypic characteristics are evaluated to determine the effect of inhibiting the expression of the candidate target gene(s). In addition, to the inhibition of gene expression at the RNA and protein levels is verified by standard methods, such as, for examples, Northern blots, QRT-PCR, Western blot, or other analytical assay, which may include time course experiments to demonstrate the efficacy and duration of inhibition for the individual genes, according to art known methods.

Transfections can result in transient expression for one to five days. Alternatively, vectors expressing RNAi can be stably expressed in cultured cells by co-transfection and selection with a dominant selectable marker, such as neomycin. As alternatives to the use of RNAi, traditional antisense DNA or vectors expressing dominant negative forms of targets of interest are used. Antisense and dominant negative genes are delivered by direct DNA transfection or through the use of virus vectors including, but not limited to, retroviruses, adenoviruses, adeno-associated viruses, baculoviruses, poxviruses, and polyomaviruses. The biological system of study chosen to demonstrate the role of a gene in disease or cellular phenotype is based upon knowledge in the art of the biological system, including a cell culture or animal model system that mimics relevant biological features.

Figure 5 illustrates the steps involved in the implementation and validation of RAS™ analysis.

Identification of Therapeutic Targets

The invention provides methods for identifying a therapeutic target by comparing the ribonomic profiles of a "test" cell sample (*e.g.*, a cell that has been treated with an agent or is derived from a diseased individual) to the ribonomic profiles of a control sample (*e.g.*, a cell that is untreated or derived from a non-diseased individual). A difference in the expression of a component of an mRNP complex between the two samples is indicative that the component is regulated by, or regulates, other components of the mRNP complex and that therefore it is a candidate therapeutic target (*e.g.*, for the up or down-regulation of that component or a component that it regulates). The therapeutic target may include, but is not limited to, any component of an mRNP complex, nucleic acid coding therefore, or gene product thereof. In an embodiment of the invention, the test cell sample is treated with a test compound and the control sample comprises cells that have not been treated with the test compound. In another embodiment, the test and control cell samples comprise cells at different stages in their growth cycle. In yet another embodiment, the test cell sample comprises a tumor cell or other diseased cell, and the control sample comprises a normal cell. Target identification includes methods known to practitioners in the art, such as, but not limited to, the use of screening libraries, peptide phage display, cDNA microchip array screening, and combinatorial chemistry techniques known to practitioners in the art. Once the mRNA or protein target has been identified, its role in a particular physiological pathway or process is assessed. For example, an mRNA or protein can be inhibited or overexpressed in a cell or organism according to standard methods. The effect of the under- or Over-expression can then be assessed by phenotypic analysis of the cell or organism. For example, RNAi may be used to knock out gene expression of the component. The gene expression of other components of the physiological pathway can be assessed, for example, using microarrays, in order to determine the regulatory effect of the altered target on other components of the process or pathway. A summary of the steps for target discovery is provided in Figure 5.

Identification of Therapeutics

In another aspect, the invention provides methods for assessing the efficacy of a test compound as a therapeutic. A cell sample is contacted with a test compound and a ribonomic profile of the cell sample comprising the expression of at least one gene product associated with at least one mRNP complex is prepared. The expression levels of the gene product(s) in the cell

sample are compared to the expression levels of the gene product(s) in a control sample (*e.g.*, a cell sample that is not contacted with a test compound). Identification of a difference in expression of the gene product between the treated and untreated cell samples is indicative that the test compound is a potential therapeutic. Test compounds may be, for example, nucleic acids, hormones, antibodies, antibody fragments, antigens, cytokines, growth factors, pharmacological agents (*e.g.*, chemotherapeutics, carcinogenics, or other cells), chemical compositions, proteins, peptides, and/or small molecules.

In various embodiments of the invention, the therapeutic may stabilize or destabilize the mRNA or the mRNP complex-associated protein. In another embodiment, the therapeutic may either inhibit or enhance translation of the mRNA, inhibit or accelerate transport of the mRNA or the mRNP complex-associated protein, inhibit the binding of the RNA binding protein to the mRNA, inhibit the binding of the RNA binding protein to the mRNP complex-associated protein, or inhibit the binding of the mRNA to the mRNP complex-associated protein, for example.

In another aspect, the invention provides methods for assessing toxicity, potential side effects, specificity or selectivity of a test compound, for example, by altering the concentrations or amounts of a test compound used to treat a cell sample.

In yet another aspect, the present invention provides methods for monitoring the efficacy of a therapeutic in a subject. In accordance with the invention, an effective amount of a therapeutic is administered to a subject. At least one mRNP complex is isolated from a cell sample from the subject, wherein altered expression of a gene product associated with the mRNP complex is altered by administration of the therapeutic. The expression of the gene product in the cell sample after administration of the therapeutic is compared to the expression of the gene product in a control sample (*e.g.*, a second cell sample obtained from the subject either prior to administration of the therapeutic or from a normal subject). The tests are repeated over a period of time to monitor the continued efficacy of the therapeutic. A difference in expression between the treated and the control cell samples is indicative of the efficacy of the therapeutic.

Therapeutics may target over- or under-expressed proteins involved in the etiology of a disease, disorder, or condition. Such over- or under-expression may result in destabilization or stabilization of RNA and/or inhibit or enhance translation of the substrate RNA.

Therapeutics that Destabilize mRNA

If a disease, condition or disorder is characterized by overexpression of a protein, a therapeutic for treatment of such a condition will reduce or eliminate expression of the protein by decreasing the stability of the RNA encoding the protein and/or by inhibiting the translation of the RNA. For example, since RNA binding proteins enhance the stability of short-lived mRNAs encoding protooncogenes, growth factors and cytokines that contribute to cell proliferation, inhibition of RNA binding protein production may alleviate diseases such as cancers or autoimmune diseases (*e.g.*, by decreasing tumor growth or inflammation, respectively). In addition, RNA binding protein overexpression in several human tumors correlates with resistance to chemotherapy and UV irradiation. Increased stability of c-fos, c-myc, cyclin B1 and other short-lived mRNAs in response to UV-irradiation or therapeutic drugs is well known. Accordingly, inhibition of RNA binding protein expression in these tumors destabilizes the mRNA in the tumors and, as a result, renders the tumors more responsive to cancer treatments.

In order to reduce overexpression or to cease expression of a protein of interest, the mRNA can be destabilized or its translation inhibited by administering an effective amount of a suitable test compound (*e.g.*, an RNA binding protein inhibitor) either *in vitro* or *in vivo*. The test compound may bind mRNA so as to inhibit RNA binding protein binding to the mRNA by binding to the RNA binding protein, bind to and destabilize the mRNP complex, and/or bind the mRNA so as to directly destabilize or inhibit the translation of the mRNA, and/or bind the RNA binding protein so as to inhibit the translation of the mRNA, for example. Compounds that bind to the mRNA but that do not stabilize the mRNA may inhibit the ability of an RNA binding protein to stabilize the mRNA or regulate translation of the mRNA. If the compound binds competitively with an RNA binding protein, the compound can decrease mRNA stability by inhibiting the RNA binding protein's ability to bind the mRNA.

Alternatively, the test compound may inhibit RNA binding protein expression or its mRNA expression.

Effective test compounds (*e.g.*, RNA binding protein inhibitors) can be readily determined by screening compounds for their ability to interfere with the production of RNA binding protein or their ability to inhibit the binding to, and/or stabilization or translation of, mRNA, for example, by methods described herein. Compounds that function by inhibiting RNA binding protein or mRNA production can be identified by exposing cells that express the RNA

binding protein or mRNA of interest and monitoring the levels of RNA binding protein or mRNA expressed, respectively. Compounds that function by inhibiting the stabilizing effect of an RNA binding protein and/or its ability to inhibit translation of an mRNA can be identified by combining RNA binding protein and an mRNA that would otherwise be stabilized, adding compounds to be evaluated as RNA binding protein inhibitors, or compounds that enhance RNA binding protein to result in inhibition of translation and monitoring the binding affinity of RNA binding protein and the mRNA. Compounds that increase or decrease the binding affinity of RNA binding protein and the mRNA can be readily determined by art known methods.

Therapeutics that Stabilize mRNA

If a disease, condition or disorder is characterized by underexpression of an mRNA stabilizing protein or results from inhibited translation of the mRNA, a therapeutic for treatment of such a medical condition may operate by stabilizing the mRNA associated with the underexpressed protein and/or enhancing the translation of the mRNA. Accordingly, mRNA may be stabilized or its translation enhanced by administering an effective amount of a compound, either *in vitro* or *in vivo*. The compound may possess a similar binding ability and stabilizing and/or translation enhancing effect as the RNA binding protein or, may promote the RNA binding protein's ability to stabilize and/or enhance the translation of the mRNA, and/or may promote the production of the RNA binding protein or the mRNA of the RNA binding protein of interest. Such a compound may be referred to as an RNA binding protein inducer and may operate by interacting with the mRNA, the RNA binding protein or both. Alternatively, mRNA can be stabilized and/or its translation enhanced by administering an effective amount of a suitable RNA binding protein that possesses the necessary mRNA stabilizing and/or translation enhancing effect.

Compounds that increase RNA binding protein production can be identified by initially exposing cells that express the RNA binding protein to potential inducers and, monitoring the levels of the RNA binding protein, in accordance with the methods described above. If the level of RNA binding protein expression increases, the compound is an RNA binding protein inducer. Compounds that inhibit RNA binding protein binding to mRNA, but which bind and stabilize and/or enhance translation of the mRNA, can be identified by methods disclosed herein. A skilled practitioner may combine RNA binding protein and an mRNA, add a compound, and monitor the binding affinity of the RNA binding protein and the mRNA. Compounds that

increase or decrease the binding affinity of an RNA binding protein and the mRNA can be readily determined by evaluating the binding affinity of the RNA binding protein to the mRNA after exposure to the compound, as described herein. By monitoring the concentration of mRNA and/or translation of mRNA over time, those compounds that bind to the mRNA can then be assayed for their ability to stabilize and/or enhance translation of the mRNA.

High Throughput Screening Methods for Libraries of Compounds

In an embodiment of the invention, high throughput screening assays and competitive binding assays are used to identify compounds that bind to an mRNP complex or component thereof from combinatorial libraries of compounds (*e.g.*, phage display peptide libraries, small molecule libraries and oligonucleotide libraries).

In one embodiment, an mRNP component, catalytic or immunogenic fragment thereof, or oligopeptide thereof, can be used to screen libraries of compounds in any of a variety of drug screening techniques. An exemplary technique is described in published PCT application W084/03584, hereby incorporated by reference. The fragment employed in such screening can be free in solution, affixed to a support, or located on a cell surface or intracellularly.

The SELEX method, described in U.S. Patent No. 5,270,163, is used to screen oligonucleotide libraries for compounds that have suitable binding properties. In accordance with the SELEX method, a candidate mixture of single stranded nucleic acids with regions of randomized sequence can be contacted with the mRNP complex. Those nucleic acids having an increased affinity to the mRNP complex can be partitioned and amplified so as to yield a ligand enriched mixture.

Phage display technology is used to screen peptide phage display libraries to identify peptides that bind to an mRNP complex or component thereof. Methods for preparing libraries containing diverse populations of various types of molecules such as peptides, polypeptides, proteins, and fragments thereof are known in the art. Phage display libraries are also commercially available.

A library of phage displaying potential binding peptides is incubated with an mRNP complex to select clones encoding recombinant peptides that specifically bind the mRNP complex or components thereof. After at least one round of biopanning (binding to the mRNP complex), the phage DNA is amplified and sequenced, thereby providing the sequence for the

displayed binding peptides. Briefly, the target, an mRNP complex, can be coated overnight onto tissue culture plates and incubated in a humidified container. In a first round of panning, approximately 2×10^{11} phage can be incubated on the protein-coated plate for 60 minutes at room temperature while rocking gently. The plates are then washed using standard wash solutions. The binding phage can then be collected and amplified following elution using the target protein. Secondary and tertiary pannings can be performed as necessary. Following the last screening, individual colonies of phage-infected bacteria can be picked at random, the phage DNA isolated and subjected to automated dideoxy sequencing. The sequence of the displayed peptides can be deduced from the DNA sequence.

The biological activity of compounds can be evaluated using *in vitro* assays known to those skilled in the art (*e.g.*, protein synthesis assays or tumor cell proliferation assays). Alternatively, the biological activity of the compounds is evaluated *in vivo*. Various compounds including antibodies, can bind to mRNP complexes and components thereof with varying effects on mRNA stability. The activity of the compounds once bound can be readily determined using the assays described herein.

Binding assays include cell-free assays in which an RNA binding protein and an mRNA are incubated with a labeled test compound. Following incubation, the mRNA, free or bound to a test compound, can be separated from unbound test compound using any of a variety of techniques known in the art. The amount of test compound bound to an mRNP complex or component thereof is then determined, using detection techniques known in the art.

Alternatively, the binding assay is a cell-free competition binding assay. In such assays, mRNA is incubated with labeled RNA binding protein. A test compound is added to the reactio and assayed for its ability to compete with the RNA binding protein for binding to the mRNA. Free labeled RNA binding protein can be separated from bound RNA binding protein. By subsequently determining the amount of bound RNA binding protein, the ability of the test compound to compete for mRNA binding can be assessed. This assay can be formatted to facilitate screening of large numbers of test compounds by linking the RNA binding protein or the mRNA to a support so that it can be readily washed free of unbound reactants. A plastic support (*e.g.*, a plastic plate such as a 96 well dish or chip) is preferred. The RNA binding protein and mRNA suitable for use in the cell-free assays described herein can be isolated from natural sources (*e.g.*, membrane preparations) or prepared recombinantly or chemically. The RNA binding protein can be prepared as a fusion protein using, for example, known recombinan

techniques. Preferred fusion proteins include, but are not limited to, a glutathione-S-transferase (GST) moiety, a green fluorescent protein (GFP) moiety that is useful for cellular localization studies or a His tag that is useful for affinity purification.

A competitive binding assay may also be cell-based. Accordingly, a compound, preferably labeled, known to bind an mRNP complex or component thereof, is incubated with the mRNP complex or component thereof in the presence and absence of a test compound. By comparing the amount of known test compound associated with cells incubated in the presence of the test compound with that of cells incubated in the absence of the test compound, the affinity of the test compound for the RNA binding protein, mRNA, and/or complex thereof can be determined. Cell proliferation can be monitored by measuring the uptake into cellular nucleic acids of labeled bases (*e.g.*, radioactively, such as ^{3}H, SiC, or ^{14}C; fluorescently, such as CYQUANT (Molecular Probes, Eugene, OR); or colorimetrically such as BrdU (Sigma, St. Louis, MO) or MTS (Promega, Madison, WI)) as known in the art. Cytosolic/cytoplasmic pH determinations can be made with a digital imaging microscope using substrates such as bis(carboxyethyl)-carbonyl fluorescein (BCECF) (Molecular Probes, Inc., Eugene, Oregon).

Other types of assays that can be carried out to determine the effect of a test compound on RNA binding protein binding to mRNA include, but are not limited to, the Lewis Lung Carcinoma assay and extracellular migration assays such as the Boyden Chamber assay.

Accordingly, the methods permit the screening of compounds for their ability to modulate the effect of an RNA binding protein on the binding of and stability of mRNA. Using the assays described herein, compounds capable of binding to mRNA and modulating the effects on those cellular bioactivities resulting from mRNA stability and correlated protein synthesis are identified. The compounds identified in accordance with the above assays are formulated as therapeutic compositions.

Diagnosing and Monitoring Disease

In another aspect, the invention provides methods for diagnosing a disease or risk of a disease related to glucose and/or lipid metabolism (*e.g.*, obesity or diabetes) or cellular function. A ribonomic profile from a subject's cell sample is prepared and at least one mRNP complex is analyzed. The expression of at least one gene product, for which altered expression is indicative of a disease or risk of disease, is determined. The gene product may be an RNA binding protein, an mRNA, an mRNP complex-associated protein or other gene product bound to or associated

with the mRNP complex. The expression of the gene product in the cell sample is compared to the expression of the gene product in a control sample. The control sample may be, for example, a sample of normal cells or a second cell sample from the subject. Alternatively, the control sample is a positive control, for example, from a diseased and/or normal individual. By observing the relative expression of the gene product in the cell sample compared to the control sample, the presence of a disease or risk of disease can be determined.

In another aspect, the invention discloses a method for monitoring a disease state in a subject. At least one mRNP complex is isolated from a diseased subject's cell sample, wherein the mRNP complex has at least one gene product that is associated with the disease. The expression of the gene product in the subject's cell sample is compared to the expression of the gene product in a control sample. The identification of a difference in the expression of the gene product in the diseased subject cell sample compared to the expression of the gene product in the control sample is indicative of a change in the disease state of the subject. For example, a decrease in the production of a tumor related antigen or its mRNA is indicative of decreased tumor load or remission; by contrast, an increase in expression of the tumor antigen is indicative of aggressive tumor growth. Such monitoring during drug treatment provides information about the effectiveness of the subject's drug regimen, and may indicate when a particular regimen is not, or is no longer, effective for treating the disease or condition. The control sample may be, for example, a second cell sample from the subject, preferably, obtained when the subject is free of one or more symptoms of the disease. Alternatively, the control sample is, for example, from a normal subject or other normal cell sample.

In summary, the present invention provides useful *in vivo* and *in vitro* methods for determining the ribonomic profile of a cell and detecting changes in the ribonomic profile. The invention has numerous uses, including, but not limited to, monitoring cell development or growth, monitoring a cell state, and monitoring perturbations of a biological system such as disease, condition or disorder. The invention further provides methods for diagnosing a disease, condition, or disorder and determining appropriate treatment regimens. The invention also is useful for distinguishing ribonomic profiles among organisms such as plant, fungal, bacterial, viral, protozoan, or animal species.

The present invention can be used to discriminate between transcriptional and post-transcriptional contributions to gene expression and to track the movement of RNAs through mRNP complexes, including the interactions of combinations of proteins with RNAs in mRNP

complexes. Accordingly, the present invention can be used to study the regulation of RNA stability. The present invention can be used to investigate the activation of translation of mRNAs as single or multiple species by tracking the recruitment of mRNAs to active polysomes measuring the sequential, ordered expression of mRNAs such as mRNAs that encode transcription factors or RNA binding proteins, and measuring the simultaneous, coordinate expression of multiple mRNAs. The present invention can also be used to determine the transacting functions of RNAs themselves upon contacting other cellular components. These and numerous other uses will be made apparent to the skilled artisan upon study of the present specification and claims.

The following Examples are set forth to illustrate the present invention, and are not to be construed as limiting thereof.

Exemplification

Example 1: Target Discovery Using Ribonomic Profiles

The general steps required for target discovery using the methods of the invention are summarized in Figure 5. Briefly, expression profiles for RNA binding proteins are generated to identify RNA binding proteins that have altered expression in different cell types, in a disease phenotype, or in response to certain stimuli, for example. Candidate RNA binding proteins may then be cloned and their cDNAs inserted into various bacterial and mammalian expression vectors for production of recombinant RNA binding proteins and overexpression of RNA binding proteins, respectively. Recombinant or purified RNA binding proteins are then used to generate monoclonal or polyclonal antibodies for use in RAS™ analysis performed on extracts from cells or tissues. Intact mRNP complexes associated with the differentially expressed RNA binding protein are then immunoprecipitated, for example, using antibodies to the RNA binding protein. Once the mRNP complex is isolated, the other components of the mRNP complex, including RNAs and other mRNP complex associated proteins, are identified and compared and characterized. Differential expression of the other components of the mRNP complex is determined in different cell types, in a disease phenotype, or in response to certain stimuli. Once differential expression is determined and candidate mRNP components are identified, their biological role, *e.g.*, participation in a certain pathway or disease, is validated by inhibition and overexpression studies. mRNP components that participate in a certain pathway are candidate therapeutic targets for diseases relating to aberrant regulation of that pathway.

Establishing Expression Profiles for RNA Binding Protein Genes

In one procedure for identifying candidate RNA binding proteins for further analysis, RNA binding protein expression profiles are generated in control or agent treated cell lines or tissues, and from normal and diseased human tissues. The agents used to treat the cells or tissues may include any agent that affects insulin action, insulin secretion glucose metabolism or lipid metabolism such as, adiponectin, leptin, resistin (or agents that act through the receptors for adiponectin, leptin, resistin), tumor necrosis factor-alpha, glucose, insulin, a beta-adrenergic agonist, insulin-like growth factor-1 (IGF-1), glucagon-like peptide-1 (GLP-1), fatty acid, peroxisome proliferator activated receptor (PPAR) ligands (*e.g.* thiazolidinediones, fibrates, halogenated fatty acids, and tyrosine derivatives), insulin-like growth factor-2 (IGF-2), RNAi against a RNA binding protein, an agent that enhances RNA binding protein expression and/or a small molecule (*e.g.*, putative drug).

Initial tissue, disease, or agent screening of RNA binding protein gene expression can be accomplished by Quantitative Real Time PCR (QRT-PCR) using oligo dT-primers and commercially available RNA samples (Stratagene, Inc., La Jolla, CA; Ambion, Inc., Austin, TX; BD Biosciences Clontech, Palo Alto, CA). 10-100μg of cDNA is used to perform Quantitative PCR (Q-PCR) using SybrGreen (Molecular Probes, Inc., Eugene, OR) and gene specific PCR primers on a BioRad iCycler Quantitative PCR machine (Biorad, Hercules, CA) using protocols provided by the manufacturer. Experimental results are analyzed using the accompanying BioRad iCycler software. RNA levels for candidate RNA binding proteins are normalized to rRNA.

In addition to the above approaches, for rapid and comprehensive screening of tissues and cell lines, a RIBOCHIP™ array (Ribonomics, Inc., Durham, NC, designed and manufactured by MWG Biotech USA, Highpoint, NC) may be used. The RIBOCHIP™ contains 50-mer oligonucleotides corresponding to RNA binding protein genes in duplicate, non-contiguous positions, plus control genes, on glass slides. The nucleic acid sequences were compiled from a wide variety of public databases and search tools including GenBank (NCBI, Bethesda, MD), PubMed (NCBI, Bethesda, MD), SRS Evolution (LION Biosciences, Cambridge, MA), LocusLink (NCBI, Bethesda, MD), Protein FAMily database (pFAM, Washington University, St. Louis, MO); Welcome Institute ; Sanger Institute (Hinxton, UK), GO Database (Gene Ontology™ Consortium, Gene Ontology: tool for the unification of biology. The Gene Ontology Consortium (2000) Nature Genet. 25: 25-29), Structural Classification of

Proteins (SCOP©), and Package (Medical Research Council, Cambridge, UK). A detailed method for microassay analysis on the RIBOCHIP™ and section of differentially expressed genes is described below.

The RNA binding proteins identified as having altered expression in response to treatments, disease, or cell cycle changes are useful for prioritizing candidates for RAS™. In addition, RNA binding proteins themselves may be candidates for therapeutic targeting and/or gene therapy (*i.e.*, gene replacement or gene silencing) or therapeutic antibody targets.

Cloning and Expression of RNA Binding Protein Genes in Bacterial Vectors

When candidate RNA binding proteins are identified, full length cDNA clones are generated by reverse transcriptase-PCR (RT-PCR) using commercial RNA tissue sources and standard methods. For example, full-length plasmid clones are constructed based on phage lambda-based (att) site-specific recombination protocols (Invitrogen, Corp., Carlsbad, CA) for the GATEWAY™ pENTRD-Topo entry vectors and pDEST17 6XHis destination vectors (Invitrogen, Corp., Carlsbad, CA) or glutathione S transferase vectors (*e.g.*, pGEX from Amersham, Piscataway, NJ). *Escherichia coli* (*e.g.*, BL21SI or BL21A1) expressing polyhistidine-tagged or GST-tagged RNA binding protein fusion proteins are grown to mid-log phase at 37°C and induced in 0.3 M NaCl for BL21SI cells or in 0.2 % mM arabinose or about 0.1mM to about 1mM IPTG for BL21A1 cells at 20-37°C for about 2-6 hours (specific time based upon optimization in pilot expression studies for each clone). Bacterial cells are lysed by sonication and the RNA binding protein-fusion protein is purified on nickel columns (Qiagen, Inc., Valencia, CA) or glutathione Sepharose (Amersham, Piscataway, NJ) using standard methods. Insoluble fusion proteins are maintained and purified in the presence of 8M urea, and soluble proteins are maintained in phosphate buffered saline (PBS). The purified fusion proteins are used for immunization of mammals (*e.g.*, rabbits, pigs, or chickens) for production of polyclonal antibodies using standard methods. Polyclonal antibodies are characterized by their ability to immunoprecipitate and detect by western blot, for example, native and recombinant proteins. The recombinant RNA binding protein is also used for *in vitro* RAS™ described below.

Analysis of Other mRNP Complex Components

Changes in the abundance or constellation of RNA binding proteins in a cell affect the processing of any mRNAs bound to those RNA binding proteins. The subset of mRNAs that are associated with an RNA binding protein is indicative of functional co-regulation that is critically or causally involved in effecting a phenotypic change in the cell. Thus, those genes whose mRNAs are associated with tissue-, disease-, or agent altered mRNP complexes are a rich source of potential therapeutic targets.

RNA binding proteins that exhibit the most dramatic variation with regard to expression proceed into the next stage of analysis, the Ribonomic Analysis System (RAS™) assay (Ribonomics, Durham, NC). The RAS™ assay uses a microarray format to identify and/or quantify the specific mRNAs associated with particular RNA binding proteins. Commercially available glass slide arrays (such as, for example, Human Unigene 14K, Agilent, Palo Alto, CA and Pan Human 10K, MWG Biotech, Inc., High Point, NC), or membrane arrays, such as, for example, ATLAS™ Arrays, BD Biosciences, Clontech, Palo Alto, CA), are employed using protocols for hybridization, washing, and development provided by the array manufacturers.

The composition of RAS™ assay lysis buffer (RLB) may vary, depending on the binding characteristics of a particular RNA binding protein. Basic RLB contains 50 mM HEPES, pH 7-7.4, 1% NP-40, 150 mM NaCl, 1 mM DTT, 100 U/ml RNase OUT (Gibco BRI, Invitrogen Corp., Carlsbad, CA), 0.2 mM PMSF (Sigman Aldrich, St. Louis, MO), 1 μg/ml aprotinin (Sigman Aldrich, St. Louis, MO) and 1 ug/ml leupeptin (Sigman Aldrich, St. Louis, MO). Variations of these basic components included changes in salt concentrations (*e.g.*, about 0 to about 500 mM NaCl or about 0 to about 5 mM KCl), ionic conditions (about 0 to about 10 mM $MgCl_2$ or about 0 to about 20 mM EDTA), and reducing environment (about 0 to about 5 mM DTT). For example, in order to prepare cell extracts for examining the polypyrimidine tract binding protein (PTB) mRNP complex, cultured cells are washed in ice-cold PBS and scraped directly into RLB containing 5 mM $MgCl_2$ and incubated on ice for 10 minutes followed by centrifugation at 3,700 xg for 10 minutes at 4 °C.

It is necessary in certain cases to crosslink the mRNP complex prior to isolation so that the RNA binding protein remains associated to its mRNAs. This is performed on cultured cells as well as fresh tissue samples. The extent of crosslinking is titrated for each cell line or tissue and monitored based on the ability to immunoprecipitate mRNA in the complex. For example,

cultured cells or tissues are incubated in PBS containing about 0 to about 1% formaldehyde at room temperature for about 15 - 60 minutes. Crosslinking is then quenched by the addition of 1M Tris pH 8.0 to a final concentration of 250 mM Tris pH 8.0 and incubated further for an additional 20 minutes. The samples are then washed 3x in PBS containing 50 mM Tris pH 8.0. For cultured cells, the cells are pelleted and resuspended in radioimmunoprecipitation (RIPA) buffer (50 mM Hepes, pH 7.4, 150 mM NaCl, 1% NP-40, 0.1% SDS, 0.5% deoxycholate (DOC) (Sigma-Aldrich, St. Louis, MO) and 100 U/ml RNase Out (Gibco BRI, Invitrogen Corp., Carlsbad, CA) to about 2 mg/ml final protein concentration. For tissues, the samples are resuspended in RIPA and homogenized with a polytron to disrupt the tissue. Following the initial lysis, the samples are subjected to sonication with a probe sonicator (Branson 450, Branson Ultrasonics Corp., Danbury, CT) at output setting 6, two times for 20 seconds each. Between sonications the samples are allowed to cool on ice for 2 minutes. Lysates are then cleared by centrifugation at 3,700 x g for 15 minutes. The next stages include immunoprecipitation and RNA extraction.

Immunoprecipitation of mRNP Complexes and RNA Extraction

On average, typical final protein concentrations for the cellular lysates are 2 mg/ml. Approximately 2 mg protein is used for each immunoprecipitation condition. Cleared cellular extracts are incubated with primary antibody (*e.g.*, an anti-PTB (Zymed, South San Francisco, CA) is used at a final concentration of 10 µg/ml) or a control antibody at equal concentration (*e.g.*, pre-immune or IgG sera (Pierce Biotechnology, Rockford, IL) at final concentration of 10 µg/ml) for 2 hours at 4°C. A 25 µl aliquot of Protein A Trisacryl beads (Pierce Biotechnology, Rockford, IL) is added and the samples rotated for 1 hour at 4°C. The immune complex is then washed 6x in RLB buffer by adding 1 ml of RLB buffer followed by brief centrifugations in a microcentrifuge for 30 seconds at 5,000 rpm. After the final wash, 50 µl of RNA extraction buffer from the PICOPURE™ RNA isolation kit (Arcturus, Inc., Mountain View, CA) is added to the beads, vortexed briefly and centrifuged to pellet the beads. The extracted RNA is purified following the PICOPURE™ protocol (Arcturus, Inc., Mountain View, CA). RNA present in the mRNP complex is then quantified using the RIBOGREEN™ assay (Molecular Probes, Inc., Eugene, OR).

Amplification of RNA for Microarray Analysis

Since mRNA isolated from mRNP complexes represents only a small subset of total RNA, isolated mRNA may be amplified prior to labeling. Message Amp™ (Ambion, Inc., Austin, TX) is used for RNA amplification according to the manufacturer's instructions. Two rounds of amplification are performed prior to labeling by random primer polymerization with Cy3 or Cy5-dUTP. Hybridization and washing are performed according to the microarray manufacturer's protocols and as described above. Microarray data acquisition and analysis are performed as described below.

Microarray Analysis

These methods are employed for analysis of RNA for ribonomic profiling with the RIBOCHIP™ as well as analysis on pan arrays with RNA extracted from the mRNP complexes to identify genes within a Ribonomics cluster.

RNA Preparation

The mRNA samples to be analyzed are prepared from various cell and tissue-types by RNA extraction with RNeasy™ (Qiagen, Inc.), quantified by absorbance (A_{260}), and stored at -80°C until use. Purified, Dnase I treated RNA was routinely analyzed using an Agilent 2100 Bioanalyzer. RNA was assessed for purity by examining electropherograms for the presence of broad peaks overlapping the 28S and 18S ribosomal RNA (rRNA) peaks. Broad peaks of this nature indicate contamination with genomic DNA. If such contamination was detected, the RNA was retreated with Dnase I and purified as described above. In addition, the relative abundance of 28S to 18S rRNA was determined to assess the quality of the RNA sample. Ratios greater than or equal to about 1.7 for 28S/18S rRNA indicate little or no degradation of the RNA and are acceptable for microarray analysis. Ratios less than about 1.7 indicate degraded RNA that is not acceptable for microarray analysis.

Synthesis of aminoallyl-UMP labeled cDNA

Aminoallyl cDNA was synthesized based on modifications of protocols by DeRisi (www.microarray.org; "Reverse Transcription and aa-UTP Labeling of RNA") and TIGR (www.tigr.org; Protocol M005). Briefly, total RNA (10 μg) was combined with 2 μl dT_{18} (200 μM), 2 μl random decamer (1 mM stock), and diethyl pyrocarbonate (DEPC) treated water to a

final volume of 17.5 µl. Primers were annealed to the RNA template by heating at 70 °C for 10 minutes and then cooling to room temperature or on ice. Aminoallyl cDNA was synthesized by addition of combining the above reaction with 6 µl SuperScript II first strand buffer, 3 ml 0.1 M dithiothreitol, 0.6 ml 50X labeling mix (25 mM dATP, 25 mM dGTP, 25 mM dCTP, 15 mM dTTP, and 10 mM aminoallyl-dUTP (Sigma; St. Louis, MO; Catalog A0410)), 1 ml RNAseOUT (Invitrogen; Carlsbad, CA; Catalog 10777-019), and 1 ml SuperScript II (Invitrogen; Carlsbad, CA; Catalog 18064-022) followed by incubation for 3 to 24 hours at 42 °C. The RNA was hydrolyzed by addition of 10 µl each 1 M NaOH and 0.5 M ethylenediamine tetraacetic acid followed by incubation for 15 minutes at 65 °C. The solution was neutralized by addition of 10 µl of 1 M HCl. The aminoallyl-cDNA was purified using Qiagen QiaQuick PCR purification kit with the following modifications. The cDNA was mixed with 5x reaction volumes of the Qiagen supplied PB buffer and transferred to a QIAquick column. The column was placed in a collection tube and centrifuged for 1 minute at 13,000 rpm. The column was washed by addition of 750 µl of phosphate wash buffer (prepared by mixing 0.5 mL 1 M KPO_4 (9.5 mL 1M K_2HPO_4 + 0.5 mL 1M KH_2PO_4), pH 8.5; 15.25 RNase free water; and 84.25 mL 95% ethanol) and centrifuging at 13,000 rpm. The wash step was repeated and the column centrifuged 1 minute at maximum speed to remove all traces of wash solution. The column was transferred to a clean collection tube and the aa-cDNA was eluted by addition of 30 µl of phosphate elution buffer (prepared by mixing 0.5 mL 1 M KPO_4, pH 8.5; 15.25 RNase free water; and 84.25 mL 95% ethanol). The elution was repeated once and the sample was dried in a speed-vac.

Coupling of Cyanin Reactive Esters to aa-CDNA and Purification of Labeled cDNA

The purified aa-cDNA was coupled to cyanine dyes (Amersham Biosciences; Piscataway, NJ; Catalog # PA23001 (Cy3) or PA25001 (Cy5)); purified; and analyzed as described. Stock solutions of Cyanin3 and Cyanin5 reactive N-hydroxysuccinamide dye were prepared by dissolving one tube of reactive dye in 73 µl of anhydrous DMSO. Reactive dye was coupled to aa-cDNA by addition of 4.5 µl reactive DMSO dye solution to the aa-cDNA and incubating for 1 hour in the dark at room temperature. Following coupling, the dye-labeled cDNA was purified using standard QIAquick PCR cleanup kit methods and buffers. The labeling reactions were analyzed for incorporation according the TIGR M005 protocol.

Hybridization and processing of Spotted Microarrays

Each spotted microarray is sufficient for analysis of two Cy-dye labeled samples, one labeled with Cy3 and one labeled with Cy5. For each microarray, material from one Cy3 labeling and one Cy5 labeling reaction were pooled and dried in a speed vac. The pooled samples were then hybridized to the microarray and the slides processed according to the general guidelines suggested by the manufacturer (MWG Biotech, High Point, NC).

Microarray Data Extraction and Analysis

Figure 6 provides a flow chart of the data extraction and analysis using microarrays. Microarrays were scanned using an Axon 4000B Scanner and GenePix version 4.0 software (Axon, Union City, CA). The resulting image files were quantified using BioDiscovery's Imagene software version 5.5 (El Segundo, CA) using standard background and spot finding settings. Two methods of data analysis were employed. The preferred method involved pre-processing the data using the BioConductor Suite (www.bioconductor.org; v 1.2) of microarray libraries for the R statistical environment (www.r-project.org; v 1.7.1). Preprocessing involved background subtraction, application of intra-array Lowess intensity and location dependent normalization, and, in some cases, inter-array scaling using the MAD function of the BioConductor normalization library. The normalized intensity data was exported for further analysis in GeneSpring (Silicon Genetics; Redwood City, CA). Within GeneSpring, differentially expressed genes were identified based on ANOVA analysis (Welch's t-test for 2 conditions) and a suitable p-value threshold. Typically, a p-value of ≤ 0.05 was employed, although this value could be increased as necessary. Additionally, one or more of the available multiple testing corrections were applied to the data to reduce the occurrence of false positives. This was not always possible, particularly if the number of replicates available was too small. An alternative and less desirable method of data analysis was also employed occasionally. This involved filtering the data based on background subtracted signal intensity (*e.g.* ≥ 500) and fold differential expression between the experimental and control samples (*e.g.* ≥ 2 fold differential from control). Routinely, genes expressed at a level above local background are considered members of that cluster. The presence of the candidate genes and their relative folds enrichment over total RNA is verified and more accurately quantified by a QRT-PCR using sequence-specific primers.

In a standard RAS™ analysis (*e.g.*, comparing normal vs. disease cells or treated vs. untreated cells), quantitative and qualitative changes in the total RNA content are compared to changes in the RNA content of the particular mRNP complex. The data obtained is routinely grouped into four classes: (1) RNAs that show comparable quantitative changes in the mRNP complex, (2) RNAs present in the total RNA but not in the mRNP complex, (3) RNAs present in the mRNP complex but apparently absent or below the level of detection in total RNA, and (4) RNAs that change in the cluster in a quantitatively different manner than in the total RNA analysis. In addition, the RAS™ assay identifies genes represented by class 4 that do not change in total abundance but that are repartitioned within the cell for alternative processing and regulation. As a result, different splice variants may be translated, the mRNA might be transported to and translated at a specific location within the cell, or translation itself might be up or down modulated. The subsets of genes identified within groups 3 and 4 cannot readily be identified by any other currently available approach to characterization of gene expression.

The methods of the invention identify genes that participate in the cellular pathways that contribute to the phenotypic changes associated with disease or certain cellular states and thus are attractive therapeutic targets. In addition, the methods of the invention identify target classes that have proven to be tractable targets for small molecule drugs. These target classes include nuclear receptors (*e.g.*, hormone receptors), G-protein coupled receptors, phosphodiesterases, kinases, proteases, and ion channels, among others. Other target classes of therapeutic interest include secreted molecules, extracellular ligands, and phosphatases.

For RNA binding proteins identified or differentially expressed on the RIBOCHIP™ and for candidate target genes or gene products identified by the RAS™ assay followed by global gene expression analysis on pan arrays, QRT-PCR was used to validate the expression at the RNA level when possible at the protein level by Western blot. For QRT-PCR, RNA is reverse transcribed to cDNA using Superscript II reverse transcriptase (Invitrogen, Carlsbad, CA, Cat# 18064-014) following the recommended kit protocol.

In 96 well PCR plates, 50ng of cDNA/well were incubated with 1X iQ sybr green supermix (Biorad, Hercules, CA. Cat# 94547) and either reaction specific or control primer pairs for a final volume of 50ul. All reactions were in duplicate. QRT-PCR reactions were run on a Biorad iCycler machine, using the sybr 2 step program (1 cycle at 95 C for 8minutes and 30 seconds; 40, 2 step cycles of 95 C for 30 seconds followed by 60 C for 60 seconds; 100 cycles of 55 C for 10 seconds). Data are compared to a normalized gene such as actin, GAPDH, or

ribosomal RNA. Differences in cycle time are used to compare and determine expression values relative to controls.

Immunoprecipitation of RNA Binding Protein Complexes

As an example of immunoprecipitation and isolation of a mRNP complex using RAS™, the PTB ribonomic cluster (referred to also as PTB-cluster or PTB functional cluster) was isolated. In this example cell extracts were prepared from INS-1 cells (BetaGene, Inc., Dallas TX) that had been stepped-down in low glucose and then stimulated with high glucose media for 2 hours as described above. Cell extracts were prepared by harvesting in RLB buffer as above. Following centrifugation, the cell extracts were brought to 300mM NaCl and 15 mM EDTA (RLB-NaCl/EDTA). The extracts (500ug protein) were incubated with 10ug α-PTB (Zymed, Cat# 32-4800) or 10ug of a control IgG (source, city, state) for 2 hours followed by a 1 hour incubation with 30µl of protein A sepharose. The immunoprecipitates were washed 6 times in RLB-NaCl/EDTA. Optimization of immunoprecipitation of other RNA binding protein and associated components would be required. In examples of optimization, pH, ionic conditions, salt concentrations, reducing environment and incubation times can be varied.

RNA was extracted and purified from the immunoprecipitates using PicoPure RNA isolation kits (Arcturus). The purified RNA was quantified by RiboGreen (Molecular Probes) analysis and integrity of the samples was determined using a BioAnalyzer (Agilent). From these analyses approximately 25-30ng of nucleic acid was associated with the control IgG immunoprecipitates. In contrast, approximately 200 – 900 ng of nucleic acid was immunoprecipitated by the PTB antibody. In order to obtain enough RNA for microarray studies, samples were subjected to two rounds of amplification using the MessageAmp kits and protocols (Ambion). Analysis of 10K Rat Pan Microarrays (MWG Ct#2250-000000) were performed as described for the RNA binding of protein arrays.

This analysis revealed a highly enriched (>5-fold) subset of approximately 450 genes. The normalized intensities of many of the genes were altered (>2-fold) in the clusters isolated from cells treated with 15mM glucose whereas the same genes in the total RNA analysis were unchanged. This suggests that glucose could regulate the appearance of many mRNAs into or out of the cluster. Numerous predicted genes were highly enriched in the PTB-cluster and the presence of many of these was regulated by glucose. Included in this list are mRNAs for Glut2, glucokinase, phosphofructokinase, Kir6.2 (the ATP-sensitive K+-channel), SUR1 (sulfonylurea

receptor 1), L-type Ca2+-channels, acyl-coa carboxylase and preproinsulin. In addition, and importantly, approximately 10% of the 450 genes in the PTB cluster had normalized intensity values at or below detectable levels when analyzed by microarray analysis of total mRNA samples. Thus, the ability to isolate the PTB cluster, purify and identify its associated mRNAs lead to the identification of very low abundant genes that most likely would have been missed or ignored in a normal array analysis. The ability to isolate the PTB cluster, enrich for a unique subset of genes, their regulated appearance in the cluster and identification of very low abundant genes supports the hypothesis regarding the role of RNA binding proteins in gene/protein expression and their utility for obtaining novel target and cellular pathway information. Expression of all candidate mRNAs in an RNP complex chosen for further downstream analysis are verified at the mRNA level by QRT-PCR using gene specific primers.

Example 2: Identification and Immunoprecipitation of Preproinsulin RNA Binding Proteins Using RIBOTRAP™

An alternative method for purifying and identifying RNA binding proteins is the RIBOTRAP™ assay (Ribonomics, Durham, NC). Two approaches for RIBOTRAP™ are described below. The first approach is an *in vitro* affinity-based assay using immobilized biotinylated oligonucleotides with sequences corresponding to RNA binding protein binding elements (Method 1). The second approach uses an affinity-tag placed on a full-length mRNA of interest or fragment of the mRNA of interest, which is expressed in a cell culture model and isolated using immobilized antibodies against the tag (Method 2).

To summarize Method 1, a cDNA representing a nucleic acid of interest or a portion of a nucleic acid that encodes an RNA binding protein binding site (*e.g.*, a 5' or 3' UTR) is cloned using standard techniques into an expression vector possessing an appropriate mammalian cell promoter (*e.g.*, a CMV, SV40, or actin promoter), or alternatively an adenovirus or retrovirus vector, and transfected into a compatible mammalian cell line. For the isolation of RNA binding proteins that participate in glucose and/or lipid metabolism, the cDNA may be expressed in a preadipocyte, adipocyte, or pancreatic beta cell line, for example. Following expression of the engineered cDNA, a cell extract is prepared that maintains the association between RNAs and their associated RNA binding proteins and mRNP complex-associated proteins, if present. The mRNA encoded by the transfected cDNA is affinity purified using an affinity protein that is known to bind to it, preferably one that does not interfere with the binding of the mRNA to its

RNA binding protein(s). The affinity protein used may be linked to a solid matrix, such as agarose or Sepharose beads, and may be biotinylated or otherwise labeled (Method 1 below). Alternatively, the affinity protein may also be bound to the solid matrix indirectly via binding to an antibody that is bound to the solid matrix (Method 2 below). The affinity protein-matrix is used to isolate the expressed RNA, along with the RNA binding proteins and/or mRNP complex-associated proteins that are associated with the mRNA *in vivo*. Variations on the two methods include chemical crosslinking of the mRNP complexes with formaldehyde or the use of an epitope tagged or beaded binding element or an epitope tagged mRNA of interest.

Proteins that are isolated in association with the mRNA of interest using the RIBOTRAP™ assay are identified using standard proteomic methods. For example, Matrix Assisted Laser Desorption/Ionization - Time-of-Flight Mass Spectrometry (MALDI TOF) and Tandem Mass Spectrometry (or Mass Spectrometry/Mass Spectrometry (MS/MS)) are used to identify peptide sequences that can be subjected to database searches. Antibodies reactive with identified RNA binding proteins or mRNP complex-associated proteins are raised in mammals according to standard methods.

Methods and Materials

Method 1: *In Vitro* Affinity-Based Assay Using Immobilized Biotinylated Oligonucleotides

Probes for affinity-purification of preproinsulin RNA binding proteins were synthesized and biotinylated with biotin-modified T (thymidine) by art known methods (*e.g.*, Ross *et al.* (1997) Mol. Cell. Biol. 17:2158-65). The probes for purification of preproinsulin RNA binding proteins were the following: a) for 3'-UTR element one 5'-gaauaaaaccuuugaaagagcacuac-3', b) for 3'-UTR element two 5'-cccaccacuacccuguccaccccucugcaaug-3', and c) for 5'-UTR element two 5'-agccctaagtgaccagctacagtcggaaaccatcagcaagcaggtcattgttccaac-3'. In addition, a negative control biotinylated probe (scrambled sequence) was used as described to identify and eliminate non-specific RNA binding proteins. The biotinylated probes were immobilized to streptavidin agarose (Pierce Biotechnology, Rockford, IL) or streptavidin magnetic beads (Dynal, Lake Success, NY) overnight in a 1M NaCl-containing buffer as described (Ross *et al.*, 1997). Beads were washed in high salt buffer to remove unbound probe, and then equilibrated in binding buffer. Cell extracts were prepared in RLB lysis buffer containing (50mM HEPES, pH 7.5, 0.5% NP-40, 150 mM NaCl, 1mM DTT, leupeptin 1ug/ml, aprotinin 1 ug/ml and PMSF, 10% glycerol, 200 units/ml RNAse Out). The lysates are centrifuged at 10,000 xg for 5 minutes and

the supernatants (approx 1mg/ml protein concentration) used in binding studies. Extracts were incubated with immobilized biotinylated probes (1-5 mg of coupled probe) for 4-12 hours at 4 °C, washed, and proteins eluted in SDS-PAGE sample buffer. After separation by SDS-PAGE bands corresponding to proteins specifically bound to probes are identified by Western blotting or protein sequencing as previously described.

To specifically confirm binding of polypyrimidine tract binding protein (PTB) to the preproinsulin 3' UTR, eluted PTB was analyzed by Western blot using commercially available PTB antibody (Figure 7). Both recombinant PTB and native PTB derived from INS-1 cell lysates was evaluated for binding. Figure 7 illustrates that PTB binds to the 3'UTR of preproinsulin but not the 5'UTR of preproinsulin.

Figure 8 illustrates the current paradigm of glucose-regulated RNA binding protein binding of PTB (also referred to as RBP1) to the 3' UTR of the preproinsulin mRNA, as well as putative binding of other unidentified PTB proteins. The 5'-UTR of preproinsulin mRNA contains a secondary (stem-loop) structure (ΔG= -10.8 kcal/mol) that is similar to structures found in other mRNAs that undergo regulation of biosynthesis at the translational level. Furthermore, the stem-loop structure is conserved in mammalian preproinsulin mRNAs. The 5'-UTR alone can function as a glucose and/or lipid response element. When both 5'- and 3'-UTRs are present, there is an even greater response to glucose. In addition, the glucose-stimulated translation is pancreatic beta cell-specific, since no glucose response is observed in non-beta cells. This strongly suggests the involvement of glucose and/or lipid regulated RNA binding proteins working via the 5'-UTR. Not to be limited to any particular theory, the data suggest a model in which at low or resting glucose levels, an RNA binding protein(s) is bound to the 5'-UTR of the preproinsulin mRNA and represses its translation. Increased nutrient concentrations (such as lipid and glucose) cause a change in the abundance or in the affinity of the RNA binding protein(s) for the preproinsulin 5'-UTR, thus relieving the repression and allowing enhanced translation of preproinsulin mRNA.

Method 2: Direct Affinity-Tagging Of mRNA With An RNA-Epitope

A direct affinity-tagging of mRNA with an RNA-epitope assay is described below. This method is based on antibody-recognition of a unique RNA stem loop structure. The well-characterized antibody α-g10 (*i.e.*, α-T7-tag) is raised against the N-terminus of a g10 fusion protein by standard methods. This antibody is used to screen a complex library of

degenerate RNAs (10^6 molecules) representing various stem loop structures. Following stringent washing conditions, a single 40 nucleotide RNA species is identified (D10) that was specifically recognized by α-g10. Upon further characterization, the D10 RNA is shown to mimic the peptide antigen; thus one can use the peptide for competition or elution. When the RNA-epitope is inserted into an mRNA, the RNA epitope-tagged mRNA can be specifically recovered from a mixture of total cellular mRNAs using α-g10. Furthermore, the antibody alone has no reactivity with total eukaryotic cellular mRNAs.

The D10 RNA-epitope tag is placed at the end of the 3'-UTR of the gene for Nkx6.1 and preproinsulin by methods well-known to the skilled artisan. This is accomplished by PCR cloning the tag into the full-length cDNAs for Nkx6.1 or preproinsulin (obtained by PCR cloning). These constructs are used for 1) generating *in vitro* transcripts for competition and affinity reagents, and 2) overexpression of Nkx6.1 or preproinsulin in a mammalian cell culture model followed by recovery of the RNA epitope-tagged mRNA from cell extracts with α-g10.

For the preproinsulin studies, the D10 RNA epitope-tagged preproinsulin cDNA as subcloned into pcDNA3.1neo and used to transfect MIN-6, α-TC1.6, and NIH3T3 cells. Transiently transfected cells as well as established stable transfectants (selected with Neo) are examined. Once expression of the tagged mRNA is confirmed by RT-PCR, extracts are prepared as described above from cells incubated in low or high glucose. Mock transfected cells are also examined.

Construction and transfection into the various cell-types of a D10 RNA epitope-tagged Nkx6.1 is performed in a similar manner. For analysis, the RNA epitope-tagged mRNAs are isolated from the extracts using immobilized α-g10. Proteins in these complexes are eluted with SDS-PAGE sample buffer or using antigenic peptide (NH_2-MASMTGGQQMGRC-COOH), which was previously shown to compete for the D10 epitope. A comparison of protein profiles obtained from the various cell extracts (including mock transfected cells) identifies unique protein bands. The eluted proteins are processed as described in Example 1 above to obtain peptide sequence. One variation on this procedure included D10-tagging of a fragment of the full-length mRNA (*e.g.*, the 5'- or 3'-UTR alone containing the D10 epitope).

A comparison of RNA binding protein expression profiles from α-TC1.6 cells, pancreatic beta cells (which express both homeodomain transcription factor Nkx6.1 mRNA

and protein), and NIH3T3 cells is performed to identify cell-type specific RNA binding proteins using RIBOMAP™. These RNA binding proteins represented candidate proteins that control Nkx6.1 expression.

RAS™ is then performed using antibodies to these candidate RNA binding proteins and the resulting functional clusters analyzed for Nkx6.1 mRNA expression. A functional cluster containing Nkx6.1 mRNA could contain other mRNAs that are coordinately regulated, and may code for proteins involved in development of the endocrine pancreas and/or pancreatic beta cell differentiation. Proteins that bind to the 5'-UTR of Nkx6.1 mRNA are also purified.

Specificity and Mapping of RNA Binding Protein Binding Elements

In order to verify potential RNA binding proteins and their binding specificity, competition experiments using immobilized binding sites (either biotinylated probes or D10 epitope-tagged probes generated by *in vitro* transcription) are performed. For example, the specific binding site is immobilized with either streptavidin agarose or α-g10 agarose and incubated with cell extracts or a recombinant RNA binding protein according to art known methods. The binding reactions are carried out in the absence or presence of increasing concentrations of control or competing non-biotinylated or non-tagged probes (synthetic oligonucleotides or oligonucleotides generated by *in vitro* transcription, as described above). Binding is analyzed by 1) electrophoretic mobility shift assays as described in the art and/or 2) SDS-PAGE followed by Coomassie staining, to detect the presence or absence of RNA binding protein bands. RAS™ may also be performed as a third verification procedure. In this case antibodies raised against the RNA binding protein are used to immunoprecipitate complexes as described above and microarray analysis is performed to identify the associated mRNAs, one of which should be the original endogenous target mRNA.

Example 3: Analysis of RNA Binding Protein Expression and Associated mRNAs in Human Adipocytes and Preadipocytes

Adipocytes have long been considered a primary location for glucose disposal and energy storage in the form of triglycerides (fat). Adipocytes also comprise critical endocrine tissue that not only responds to insulin through glucose uptake and lipogenesis, but also synthesizes and secretes a variety of signaling molecules involved in systemic energy homeostasis. An analysis

of RNA binding proteins and their associated mRNAs and mRNP complex-associated proteins and their role in gene expression in adipocytes provides a better understanding of adipocyte function and can identify targets for therapeutics that treat conditions associated with aberrant glucose or lipid metabolism. A flow chart for an exemplary adipocyte analysis is provided in Figure 9.

RNA binding proteins that are enriched in mature adipocytes vs. preadipocytes in lean individuals (BMI < 24) were identified as follows. Briefly, human preadipocytes were harvested from elective liposuction from three lean individuals according to standard procedures. A portion of the preadipocytes were differentiated in culture to mature adipocytes (Zen-Bio, Durham, NC). The expression pattern of RNA binding proteins in mature adipocytes was compared to the expression pattern of RNA binding proteins in preadipocytes using a RIBOCHIP™ V.1 array (MWG Biotech, High Point, NC) according to the methods described in Example 1. Figure 10 provides a list of the RNA binding proteins and corresponding genes that are differentially regulated in adipocytes vs. preadipocytes. In another experiment, the RNA binding protein expression in preadipocytes from obese individuals was compared to expression in mature adipocytes in obese individuals. Preadipocytes and adipocytes were obtained from obese individuals as described above. RNA binding proteins were identified using RIBOCHIP™ analysis as described in Example 1. Figure 11 provides a list of 14 RNA binding proteins and their corresponding genes that were induced 2 fold or more in mature adipocytes from obese individuals as compared to preadipocytes from obese individuals.

The effects of insulin or the beta 3 agonist, BRL-37344, on RNA binding protein expression in human mature adipocytes was also examined. Mature adipocytes from lean individuals were obtained as described above and either left untreated (basal) or treated with 100 nm insulin or 1μM BRL-37344 and RNA prepared from these cells (Zen-Bio, Durham, NC). Differential expression of RNA binding proteins were identified using RIBOCHIP™ analysis as described above. Figure 12 provides a list of the RNA binding proteins and corresponding genes that are differentially regulated in response to treatment with BRC-37344. Figure 13 provides a list of the RNA binding proteins and corresponding genes that are differentially regulated in response to insulin.

In addition, the expression pattern of RNA binding proteins in mature adipocytes from three lean individuals was compared to the expression pattern of RNA binding proteins in mature adipocytes from three obese individuals (BMI > 30). Preadipocytes were obtained by elective

liposuction and cultured as described above. Adipocytes from obese individuals showed an altered pattern of RNA binding protein expression.

These data provide a refined list of candidate RNA binding proteins for further validation for participation in an adipocyte pathway, insulin production or insulin action, insulin resistance, a lipogenesis pathway, diabetes, obesity, and/or glucose and lipid metabolism pathway, or any pathway that participates in an aspect of glucose and lipid metabolism, and for the isolation of associated mRNP complex-associated proteins, and associated RNAs.

Example 4: Analysis of RNA Binding Protein Expression in Rat Pancreatic Beta Cells Treated with Glucose

The effect of glucose on RNA binding protein expression in rat pancreatic beta cells was examined. A derivative of the INS-1 rat pancreatic beta cell line, clone 832/13, was chosen because of its ability to mimic many of the normal functions of beta cells of pancreatic islets. Whereas INS-1 cells respond to glucose treatment with a 2-4 fold increase in insulin secretion, clone 832/13 is induced 8-13 fold by glucose treatment.

Briefly, 832/13 cells were grown RPMI containing 10% fetal bovin serum (Invitrogen, Corp., Carlbad, CA) to near confluence, shifted to low glucose (3mM) for 1 hour, and treated for 2 hours with fresh medium containing 3mM or 15mM glucose. RNA was prepared and differential gene expression of the RNA binding proteins was determined using the RIBOCHIP™ as described abvove. Figure 14 provides a list of RNA binding proteins and their corresponding genes that displayed a 2-fold up- or down-regulation as a result of glucose treatment.

These data provide a refined list of candidate RNA binding proteins for further validation for participation in an adipocyte pathway, insulin production or insulin action, insulin resistance, a lipogenesis pathway, diabetes, obesity, and/or glucose and lipid metabolism pathway, or any pathway that participates in an aspect of glucose and lipid metabolism, and for the isolation of associated mRNP complex-associated proteins, and associated RNAs.

Example 5: Identification of Differentially Expressed RNA Binding Proteins in HepG2 Cells in Response to Peroxisome Proliferator Activated Receptor Ligands

The effects of peroxisome proliferator activated receptor (PPAR) ligands on human RNA binding protein expression was examined in the human hepatocyte cell line HepG2. Liver is a

major insulin target tissue and one of the PPAR receptors, PPARγ, is thought to be the major biological target for a number of insulin sensitizing agents, including thiazolidinediones, L-tyrosine derivatives, halogenated fatty acids and prostaglandins. The compounds profiled include prostaglandin J2, perfluorooctanoic acid, 2-bromohexadecanoic acid, Ciglitazone, Troglitazone, GW-9662, MCC-555, Wyeth 14643, and Bezafibrate. Profiling the effects of these compounds using the RIBOCHIP™ was expected to reveal changes in regulatory genes important for the pharmacological and toxicological properties associated with these agents. Common themes or patterns in gene expression likely represent common pharmacology and toxicology while distinct gene expression changes elicited by individual compounds or subsets of compounds likely represent unique pharmacological or toxicological properties. The changes in gene expression identified in this manner are therefore attractive candidates for validation surrounding participation in the mechanism of insulin action and the pharmacological and toxicological properties of PPARγ ligands.

Briefly, HepG2 cells (obtained from ATCC (www.atcc.org; catalog number HB-8065)) were maintained as recommended in Minimal Essential Medium (MEM) with 10% fetal bovine serum (FBS) supplemented with antibiotics in p150 plates at 37 °C, 5% CO_2. Cells were split 1:5 and fresh media added every 3 days. Cytotoxicity was assessed using the Alamar Blue-based CellTiter™ Blue Cell Viability Assay (Promega; Madison WI) to determine the viable cell fraction that remained following a 72 hour period. Cells (~8,000 cells/well) were plated in 96 well BioCoat collagen coated plates (Becton Dickinson; Bedford, MA) using standard media. This allowed untreated control samples (0.25% DMSO) to be in late log phase (~70% confluent) at completion of the study. Cells were then allowed to recover for 24 hours at 37 °C, 5% CO_2. A two (2) fold dilution series was prepared for each compound starting at 3.0 mM in MEM containing 0.1% BSA (instead of 10% FBS) but without phenol red or antibiotics. Following the cell recovery period, the media was removed and fresh media containing compound was added. Treatments were performed in triplicate for each compound at each dose. Cells were incubated with compound for 72 hours at 37 °C, 5% CO_2. The viable cell fraction remaining was determined by washing the wells with fresh media without indicator, lysis of the remaining live cells by addition of 0.9% Triton X-100 in water, and performing the Alamar Blue assay as described in the CellTiter™ Blue Cell Viability Assay product literature. The concentration resulting in 50% cell death relative to a vehicle only control following 72 hours of treatment (LD_{50}) was determined using Prism 4.0 (GraphPad; San Diego, CA) dose-response analysis.

RNA for microarray analysis was obtained from cells treated for 24 hours at the determined LD_{50}. Typically, ~1. 5 x 10^6 cells were plated in a p100 dish and allowed to settle for 24 hours by incubation at 37 °C, 5% CO_2 in MEM + 10% FBS without antibiotics. Old media was removed and fresh MEM + 0.1% BSA without antibiotics containing compound at LD_{50} concentration and 0.25% DMSO was added to the flask. A vehicle only treatment was also performed. Duplicate treatments were performed for each compound as well as for vehicle only controls. The cells were incubated with compound for 24 hours at 37 °C, 5% CO_2 following which they were harvested by scraping (without trypsinisation) and centrifugation. The cells pellets were flash frozen and stored at -80 °C until ready for RNA extraction.

Total RNA was extracted and analyzed for using the RIBOCHIP™ as described in Example 1. ANOVA analysis (p-value ≤ 0.05) was used to identify genes that were differentially expressed for each treatment compared to a vehicle only control (0.25% DMSO). Figures 15-22 provide lists of RNA binding proteins and their corresponding genes that are differentially expressed in HepG2 cells treated with bezafibrate (Figure 15), Wyeth 14642 (Figure 16), troglitazone (Figure 17), MCC-555 (Figure 18), ciglitazone (Figure 19), 2-bromohexadecanoic acid (2-BHDA) (Figure 20), prostaglandin J2 (PJ2) (Figure 21), and perfluorooctanoic acid (PFOA) (Figure 22).

Example 6: *In Vitro* RAS™ Identification Of mRNAs Associated With Polypyrimidine Tract Binding Protein Complexes Using the Purified Recombinant RNA Binding Protein

As and alternate approach to *in vivo* RAS™ performed using antibodies against the endogenous RNA binding protein or epitope-tagged RNA binding proteins, an *in vitro* RAS™ was used. In brief, cytoplasmic extracts from cells or tissues or purified RNA from cell or tissues is incubated with a purified recombinant RNA binding protein immobilized on a solid support. The example given below is an *in vitro* RAS™ assay performed using GST-PTB and purified RNA or cytoplasmic extracts prepared from INS-1 cells.

Cloning and Expression of RNA Binding Protein Genes that Regulate Insulin

The human PTB cDNA was cloned into a pGEX4T vector, which contains a GST affinity tag, and expressed in *E. coli* cells. The GST-PTB fusion protein was purified from bacterial lysates using the GST affinity tag, as described above.

Isolation of RNAs that Bind to PTB *In Vitro*

INS-1 cells were cultured as described in Example 2. Cells were placed on ice, washed 3 times with ice cold PBS and lysed in 1ml/dish of lysis buffer (50mM Hepes, pH 7.2, 0.5% NP40, 150mM NaCl, 2mM $MgCl_2$, 5% glycerol, 1mM DTT, 10ug/ml Aprotinin, 1ug/ml Leupeptin, 0.2mg/ml PMSF and 200U/ml RNAseOUT (Invitrogen, Carlsbad, CA. Cat# 10777-019). Cytosolic fractions were isolated by centrifuging the lysates at 3700g for 10 minutes at 4 °C. The supernatant was transferred to a fresh tube and the NaCl concentration was raised to 300mM and EDTA added for a final concentration of 20mM. This sample was then centrifuged at 10000g for 10 minutes at 4 °C. The supernatant is considered the cytoplasmic extract containing mRNA. As an additional sample, RNA is also purified from these extracts using Qiagen kits as previously described.

The GST-PTB fusion protein was used to screen for mRNAs that bind to PTB. Briefly, the purified GST-PTB fusion protein was bound to a glutathione sepharose (Amersham, Uppsala, Sweden. Cat# 17-0756-01) support through the GST linkage according to standard methods.

Purified RNA or cytoplasmic lysates containing mRNA were incubated with the bead-bound GST-PTB fusion protein for 2 hours at 4°C. RNAs that bind to GST-PTB were retained on the beads. Ionic conditions for binding and washing were altered to select for high affinity binding of mRNAs to PTB or other RNA binding proteins, as described above. In this case, beads were washed 5 times with binding buffer (50mM Hepes, pH 7.2, 0.5% NP40, 300mM NaCl, 20mM EDTA, 2mM $MgCl_2$, 5% glycerol, 1mM DTT, 10ug/ml Aprotinin, 1ug/ml Leupeptin and 0.2mg/ml PMSF). After the final wash, the beads were resuspended in 350ul of RNAeasy mini prep buffer RLT and purified RNA using RNAeasy mini prep protocol (Qiagen, Valencia, CA. Cat# 74104). Alternatively, bound mRNAs are selectively eluted with 10mM glutathione (Sigma, St. Louis, MO), according to standard methods, which competes with GST to displace the mRNA-RNA binding protein complexes from the beads. Glutathione elution enables the selective elution of only those mRNAs that are bound to the RNA binding protein, and minimizes contamination with mRNAs that are non-specifically associated with the sepharose matrix. As a positive control, eluted mRNAs were enriched for the presence of preproinsulin mRNA, which was directly assessed using QRT-PCR, according to standard

methods. The eluted and purified RNAs are then identified by microarray analysis as described in Example 1. Figure 23 provides a list of genes bound to purified recombinant GST-PTB.

RAS™ Performed With An Epitope-Tagged RNA Binding Protein Expressed In Cells Or Tissues

As an alternative approach to *in vivo* RAS™ using antibodies against the endogenous RNA binding protein or to *in vitro* RAS™, epitope-tagged versions of RNA binding proteins are expressed in a cell or tissue of interest. For example, a T7-epitope tagged PTB (T7-PTB) is transfected and expressed in INS-1 cells. The addition of the epitope tags streamlines the ability to immunoprecipitate the RNP complexes from the cells, since under most circumstances the epitope is not buried within the complex. Following stable selection of T7-PTB, mRNP complexes containing the T7-PTB are isolated from cell extracts using RLB buffer as described and the T7 monoclonal antibody (Novagen, Madison, WI). RNA is extracted and identified by microarray analysis as described.

The combined *in vitro* and *in vivo* analysis of RNP complexes offers a powerful approach to the study of post-transcriptional regulation. The comparative analysis identifies the set of genes being coordinately regulated in a variety of approaches. For the genes associate with PTB in INS-1 cells, these data provide a roadmap of the regulatory, metabolic, and signaling pathways that act in concert to orchestrate the proper production and secretion of insulin, for example. Analysis of dynamic changes in the PTB mRNP complex has lead to the identification of novel diagnostic biomarkers and a collection of compelling therapeutic targets for modulating insulin production or other gene involved in glucose and/or lipid metabolism, insulin action, insulin resistance, diabetes and obesity.

Example 7. Validation of potential therapeutic targets and components of cellular pathways by RNAi-mediated silencing of genes

Once genes within a ribonomic cluster are identified, in order to validate them as a potential therapeutic target or to place them in cellular pathways, RNAi-mediated gene silencing was performed to verify their importance in the mRNP complex. SMARTPOOL™ designed siRNAs (Dharmacon (Lafayette, CO) were used, which containa mixture of siRNAs that specifically targeted a gene of interest, resulting in a greater than ≥50% reduction in the target mRNA within 24h post-transfection.

SMARTPOOL™ siRNAs the ion channel nucleic acids that had previously not been associated with glucose-stimulated insulin secretion, included CNCG (cat# M-003833-00-05), CaCNA2D1, KCNC3 (cat#M-003838-00-05), and KCNB2 (cat#M-003830-00-05). Transfection of each siRNA was performed in INS-1 cells that were plated in 24-well culture dishes, and incubated with fresh RPMI media containing 10% fetal bovine serum 90 minutesprior to transfection. TransitTKO transfection reagent (Dharmacon, Lafayette,CO), 2 µl, was incubated for 15 minute at room temperature with SMARTPOOL™ siRNAs at a concentration range to yield a final concentration of 1-50 nM siRNA on the cells. After a 24 hour incubation at 37°C, the cells were processed for total RNA isolation and glucose-stimulated insulin secretion. Expression of target genes in untreated, control transfected and sequence-specific siRNA-transfected cells was assessed by QRT-PCR and/or immunoblotting. For insulin secretion, cells were incubated for 60 minutes in serum-free media containing 3mM glucose. The media was then changed to fresh media containing either 3mM glucose or 15mM glucose and incubated for 120 minutes. Conditioned media from each sample was then used to determine the levels of secreted insulin using an insulin ELISA (Linco Research Products, St. Charles, MO Cat#EZHI-14K). Compared to cells transfected with the control siRNA, transfection of INS-1 cells with siRNA to PTB (Figure 24A), CNCG (Figure 24B), KCNC3 (Figure 24B), KCNB2 (Figure 24B) and CaCNA2D1 (Figure 24C) showed altered insulin secretion suggesting that these are involved in the insulin secretory pathway (Figure 19). In addition, extensive time course experiments, glucose dose response experiments, and experiments that determine the ability to respond to other secretagogues, such as sulfonylureas, GLP-1 and fatty acids, can be performed.

RNAi-mediated gene silencing of the two potassium channels KCN3 and KCNB2 caused an extreme increase in basal insulin secretion levels, suggesting these channels play a functional role in the process. These two potassium channel proteins were not previously implicated in regulating insulin secretion or pancreatic beta cell function. This is significant, since the action of a class of diabetes drugs (sulfonyureas or gliburides like GLUCOVANCE) act by inhibiting a K^+ channel on the pancreatic beta cell. This inhibition leads to membrane depolarization, which allows calcium to enter the cell and stimulate release of intracellular secretory granules filled with insulin. These drugs act by increasing overall and basal insulin secretion, thereby controlling high glucose levels (hyperglycemia).

These results suggest that there are additional K^+ channels that may work in this process and provide candidate targets for new diabetes drugs.

It is notable that many of the ion channel proteins identified on the PTB cluster were not previously identified as participating in glucose and lipid metabolism. These proteins represent targets for new therapeutics that may be used to regulate a pathway that participates in glucose and lipid metabolism or other pancreatic beta cell function. Figure 25 illustrates some of the known pathways that participate in insulin secretion in pancreatic beta cells, indicating some of the proteins encoded by mRNAs found on the PTB cluster.

Over-expression of Target Proteins

Alternatively, cells can be transfected with nucleic acids encoding target proteins or treated with a transcriptional enhancer for a gene encoding a target protein of interest, in order to overexpress a particular target protein identified by the methods of the invention. These systems would then be subject to biological assays (*e.g.*, glucose-stimulated insulin secretion) as described above.

Example 8: RIBOTRAP™ Characterization of PTB on the 3'-UTR of Preproinsulin mRNA

RIBOTRAP™ experiments were performed in order to characterize the effect of glucose on the binding of PTB to the 3'UTR of preproinsulin.

Preparation of Cell Extracts: INS-1 cells were incubated in RPMI media containing 0.5 mM glucose for 2 hours. The cells were washed and the medium replaced with RPMI containing either 0.5 mM (low glucose) or 15 mM (high glucose) for various times up to 2 hours. The cells were washed with cold PBS and harvested in 1 mL RLB lysis buffer (50mM HEPES, pH 7.5, 0.5% NP-40, 150 mM NaCl, 1mM DTT, leupeptin 1μg/ml, aprotinin 1 μg/ml and PMSF, 10% glycerol, 200 units/ml RNAse Out). The lysates were centrifuged at 10,000 x g for 5 minutes and the supernatants (approx. 1mg/ml protein concentration) were used in binding studies.

RIBOTRAP™ Binding Study: A biotinylated RNA oligonucleotide probe specific for the 3'-UTR of preproinsulin, 5'-gcccaccacuacccugaccaccccucugcaaugaauaaaaccuuugaaagagc-3', and a biotinylated control RNA oligonucleotide probe, 5'-ugaauacaagcucacgacccacuacacaagcuaccagauacaacaacaagcauccacc-3' were prebound to

streptavidin agarose beads according to standard methods. For PTB binding, the salt concentration of INS-1 cell extracts was adjusted to 300 mM NaCl and 10-100 µl cell extract was incubated with the biotinylated oligonucleotide probes (1-50 µg) for 30 minutes to 12 hours. The beads were washed in RLB binding buffer (RLB/300mM NaCl) and bound protein eluted in SDS-PAGE sample buffer according to standard methods. Detection of bound PTB by immunoblotting was carried out using a monoclonal antibody against PTB (Zymed, South San Francisco, CA). Figure 26 shows the results of the immunoblot probed with the α-PTB monoclonal antibody, and indicates that glucose stimulates an acute but transient increase in PTB binding to the preproinsulin 3'-UTR. No binding was detected using the control RNA oligonucleotide.

Example 9: Identification of PTB Ribonomic Cluster using RAS™

The PTB ribonomic cluster was isolated and characterized using RAS™. Cell extracts were prepared from INS-1 cells that had been stepped-down in low glucose and then stimulated with high glucose media for 2 hours as described above in Examples 7 and 8. Cell extracts were prepared by harvesting cells in RLB buffer as described in Example 7. Following centrifugation, the salt concentration of the cell extracts was adjusted to 300 mM NaCl and 15 mM EDTA (RLB/NaCl/EDTA). These extracts (500µg protein) were incubated with 10µg of the anti-PTB monoclonal antibody α-PTB (Zymed, Cat# 32-4800, South San Francisco, CA) or 10 µg of a control IgG (Pierce Biotechnology, Rockford, IL) for 2 hours, followed by a 1 hour incubation with 30 µl of protein A sepharose (Pierce Biotechnology, Rockford, IL). The immunoprecipitates were washed 6 times in RLB/NaCl/EDTA. RNA was extracted and purified from the immunoprecipitates using PicoPure RNA isolation kits (Arcturus, Mountain View, CA). The purified RNA was quantified by RiboGreen analysis (Molecular Probes, Eugene, OR) and the integrity of the samples was determined using a BioAnalyzer (Agilent, Palo Alto, CA). From these analyses, approximately 25-30 ng of nucleic acid was associated with the control IgG immunoprecipitates. In contrast, approximately 200 – 900 ng of nucleic acid was immunoprecipitated by the PTB antibody. In order to obtain enough RNA for microarray studies, samples of approximately 500ng were subjected to two rounds of amplification using the MessageAmp kits and protocols (Ambion, Austin, TX) as described by the manufacturer. Microarray analysis was performed as described in Example 1.

For purposes of examining potential therapeutic targets from the PTB-cluster, genes with ≥ 5X enrichment compared to amplified total RNAs were sorted into the drug target classes and are listed in Figure 27.

Example 10: Use of RNAi-mediated Gene Silencing of RNA Binding Proteins to Characterize RBP Clusters

RNAi was used to inhibit PTB expression and to examine the effect of RNAi-mediated down-regulation of PTB expression on the expression of several genes within the PTB-cluster. INS-1 cells were plated in 24-well culture dishes, and incubated with fresh RPMI media containing 10% fetal bovine serum. TransitTKO transfection reagent (Dharmacon, Lafayette,CO), 2 µl, was incubated for 15 minute at room temperature with SmartPool™ siRNAs (Dharmacon, Lafayette,CO, Cat# M-003841-00-05) targeted specifically to PTB at a concentration range to yield a final concentration of 1-50 nM siRNA on the cells. After a 24 hour incubation at 37°C, total RNA was isolated and used in QR-TPCR analysis. Figure 28 illustrates the effect of PTB inhibition on the expression of PTB, preproinsulin, and nine additional genes found within the PTB-cluster. As indicated in Figure 28A, there was an 80% reduction in PTB mRNA expression, confirming the action of the PTB specific RNAi. In addition, CACNA1S, CACNA2D1, Casr, C1c3, Kcnj6, AND Loc245960 and were significantly down-regulated as a result of PTB knockdown. Figure 28B illustrates genes whose expression was up-regulated as a result of PTB knockdown. This includes insulin, which is up-regulated 3-fold.

Equivalents

The invention may be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are therefore to be considered in all respects illustrative rather than limiting on the invention described herein. Scope of the invention is thus indicated by the appended claims rather than by the foregoing description, and all changes that come within the meaning and range of equivalency of the claims are intended to be embraced therein.

Incorporation by Reference

All publications and patent documents cited in this application are incorporated by reference in their entirety for all purposes to the same extent as if the contents of each individual publication or patent document was incorporated herein.

We claim:

1. A method of identifying a therapeutic target, the method comprising the steps of:

(a) measuring protein or RNA levels of at least one component of an isolated mRNA ribonucleoprotein (mRNP) complex in a first sample enriched for a cell comprising a first phenotype; and

(b) comparing the levels determined in step (a) to the levels of the protein or RNA levels of the component in a second sample enriched for a cell comprising a second phenotype,

wherein if the levels of the component in the first sample are different from the levels of the component in the second sample, the component, a nucleic acid that encodes the component, or a protein encoded by the component is a potential therapeutic target for the treatment of a disease.

2. The method of claim 1, wherein the cell comprising the first phenotype is selected from the group consisting of a mature adipocyte, a preadipocyte, pancreatic beta cell, a hepatocyte, a skeletal muscle cell, and a cardiac muscle cell.

3. The method of claim 1, wherein the cell comprising the first phenotype is a mature adipocyte and the cell comprising the second phenotype is a preadipocyte.

4. The method of claim 1, wherein the first phenotype is a disease related to glucose or lipid metabolism and the second phenotype is a normal phenotype.

5. The method of claim 1, wherein the first phenotype is selected from the group consisting of obesity, diabetes, hypoglycemia, glucotoxicity, lipidtoxicity, insulin-resistance, hyperlipidemia, and lipodystrophy.

6. The method of claim 1, wherein the component is selected from the group consisting of an RNA binding protein, an RNA, and an mRNP-associated protein.

7. The method of claim 1, the method further comprising the step of:

(c) treating the sample in step (a) with an agent prior to measuring the protein or RNA levels of the component, wherein the agent alters the levels of at least one component of a glucose metabolic or a lipid metabolic pathway.

8. The method of claim 7, wherein the agent is selected from the group consisting of insulin, glucose, insulin-like growth factor-1 (IGF-1), a β-adrenergic agonist, glucose, glucagon-like peptide-1 (GLP-1), fatty acid, a peroxisome proliferator activated receptor (PPAR) ligand, and insulin-like growth factor 2 (IGF-2).

9. The method of claim 7, wherein the agent is a test therapeutic.

10. The method of claim 7, wherein the agent is selected from the group consisting of a nucleic acid, a protein, a peptide, or a small molecule.

11. The method of claim 1 or 7, further comprising the step of isolating the component, a nucleic acid encoding the component, or a protein encoded by the component.

12. The method of claim 1, wherein the component is Polypyrimidine Tract Binding Protein.

13. The method of claim 1, wherein the RNA binding protein is selected from the group consisting of the RNA binding proteins identified in Figure 10 to Figure 22.

14. The method of claim 1, wherein the component comprises a tag.

15. The method of claim 1, wherein the component is an mRNA that encodes a protein selected from the group consisting of a kinase, a transporter, a phosphatase, channel protein, a protease, a receptor, a transcription factor, and a transferase.

16. The method of claim 1, wherein the component is selected from the group consisting of 3-phosphoinositide dependent protein kinase-1, nuclear ubiquitous casein kinase 2, neural receptor protein-tyrosine kinase, MAP-kinase activating death domain, AMP-activated protein kinase beta-2 regulatory subunit, calcium/calmodulin-dependent protein kinase IV, Protein kinase C beta, adenylate kinase 3, mitogen activated protein kinase kinase 5, 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 2, phosphatidylinositol 4-kinase, Glucokinase, glycogen synthase kinase 3 beta, phosphorylase kinase (gamma 2, testis), protein tyrosine phosphatase (non-receptor type 1), protein tyrosine phosphatase (non-receptor type 5), inositol polyphosphate-5-phosphatase D, Protein tyrosine phosphatase (receptor-type, zeta polypeptide), dual specificity phosphatase 6, protein tyrosine phosphatase (non-receptor type 12), glucose-6-phosphatase (catalytic), 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 2, proton gated cation channel DRASIC, Sodium channel (nonvoltage-gated 1, alpha (epithelial)), calcium

channel (voltage-dependent, alpha2/delta subunit 1), Potassium inwardly-rectifying (channel, subfamily J, member 6), potassium channel regulator 1, calcium channel (voltage-dependent, T type, alpha 1G subunit), cyclic nucleotide-gated cation channel, amiloride-sensitive cation channel 1, potassium inwardly-rectifying channel J14, potassium large conductance calcium-activated channel (subfamily M, alpha member 1), potassium voltage gated channel (Shab-related subfamily, member 2), potassium channel subunit (Slack), potassium intermediate/small conductance calcium-activated channel (subfamily N, member 1), Sodium channel (voltage-gated, type V, alpha polypeptide), amiloride-sensitive cation channel 2 (neuronal), potassium channel (subfamily K, member 6 (TWIK-2)), cation-chloride cotransporter 6, solute carrier family 21 (organic anion transporter, member 12), amino acid transporter system A2, peptide/histidine transporter, choline transporter, solute carrier family 31 (copper transporters, member 1), solute carrier family 13 (sodium-dependent dicarboxylate transporter), solute carrier family 2 (facilitated glucose transporter, member 13), solute carrier family 12 (potassium-chloride transporter, member 5), Solute carrier family 6 (neurotransmitter transporter, serotonin, member 4), Solute carrier family 2 A2 (glucose transporter, type 2), carboxypeptidase D, ubiquitin specific protease 2, mast cell protease 1, proprotein convertase subtilisin / kexin, type 7, laminin receptor 1 (67kD, ribosomal protein SA), protein tyrosine phosphatase (non-receptor type 1), calcium-sensing receptor, neural receptor protein-tyrosine kinase, glutamate receptor (metabotropic 4), nuclear receptor subfamily 4 (group A, member 2), Neuropeptide Y5 receptor, protein tyrosine phosphatase (non-receptor type 5), insulin-like growth factor 1 receptor, Protein tyrosine phosphatase (receptor-type, zeta polypeptide), nuclear receptor subfamily 4 (group A, member 3), glutamate receptor (metabotropic 1), Tumor necrosis factor receptor superfamily (member 1a), insulin receptor, gamma-aminobutyric acid receptor associated protein, protein tyrosine phosphatase, non-receptor type 12, cholinergic receptor (nicotinic, beta polypeptide 1), olfactory receptor (U131), Gamma-aminobutyric acid receptor beta 2, glial cell line derived neurotrophic factor family receptor alpha 1, Glycine receptor beta, glutamate receptor interacting protein 2, adenylate cyclase activating polypeptide 1 receptor 1, asialoglycoprotein receptor 2, adenosine A3 receptor, Fibroblast growth factor receptor 1, nuclear receptor binding factor 2, purinergic receptor P2Y (G-protein coupled 1), nuclear receptor subfamily 1 (group H, member 4), peroxisome proliferator activator receptor(gamma), 5 hydroxytryptamine (serotonin) receptor 4, retinoid X receptor gamma, insulin receptor-related receptor, putative N-acetyltransferase Camello 4, lecithin-retinol acyltransferase, Phenylethanolamine N-methyltransferase, fucosyltransferase 2, Sialyltransferase 8 (GT3 alpha 2,8-sialyltransferase) C, UDP-

glucuronosyltransferase, alpha 1,3-fucosyltransferase Fuc-T (similar to mouse Fut4), diacylglycerol O-acyltransferase 1, signal transducer and activator of transcription 3, ISL1 transcription factor (LIM/homeodomain), and oligodendrocyte transcription factor 1.

17. The method of claim 16, wherein the protein is encoded by a gene selected from the group consisting of CNCG, CACNA2D1, KCNC3, and KCNB2.

18. A method for identifying a therapeutic target for the treatment of aberrant glucose metabolism or lipid metabolism, the method comprising the steps of:

(a) measuring RNA or protein levels of at least one component of an isolated mRNP complex in a first cell sample; and

(b) comparing RNA or protein levels determined in step (a) to the RNA or protein levels of the component from a second cell sample,

wherein if the levels of the component in the first sample are different from the levels of the component in the second sample, the component, a nucleic acid that encodes the component, or a protein encoded by the component is a potential therapeutic target for the treatment of the disease.

19. The method of claim 18, wherein the first cell sample is from an individual at risk of having a disease or who has a disease and the second cell sample is from a normal or healthy individual.

20. A method for identifying a therapeutic target related to the treatment of a disease, the method comprising the steps of:

(a) measuring RNA or protein levels of at least one component of an isolated mRNP complex in a sample that has been treated with an agent that alters the expression of a component of a glucose metabolic or lipid metabolic pathway; and

(b) comparing RNA or protein levels determined in step (a) to the RNA or protein levels of the component in an untreated control sample,

wherein if the levels of the component in the first sample are different from the levels of the component in the second sample, the component, a nucleic acid that encodes the component, or a

protein encoded by the component is a potential therapeutic target for the treatment of the disease.

21. A method for identifying a gene or gene product involved in a physiological pathway in a cell, the method comprising the steps of:

a. isolating an mRNP complex comprising at least one component that participates in a physiological pathway;

b. identifying at least one additional component of the isolated mRNP complex,

wherein the additional component is also involved in a physiologicalpathway.

22. The method of claim 21, wherein the physiological pathway comprises a metabolic pathway or a regulatory pathway.

23. The method of claim 21, further comprising the step of confirming the activity of the additional component by inhibiting the expression of the additional component in a cell and determining the effect of the inhibition on metabolism.

24. The method of claim 23, wherein the inhibition step comprises inhibiting gene expression of the additional component using an agent selected from the group consisting of an RNAi, an antisense RNA, a ribozyme, and a PNA.

25. A method for identifying an agent that alters a physiological pathway, the method comprising the steps of:

a. subjecting a cell sample to an agent;

b. isolating an mRNP complex comprising at least one component that participates in a physiological pathway from the sample;

c. measuring the RNA or protein levels of at least one component of the isolated mRNP complex,

d. comparing the RNA or protein levels of step (c) to the RNA or protein levels of the component isolated from an untreated control sample,

wherein differential expression of the component in the agent-treated sample compared to the untreated control sample is indicative that the agent regulates the physiological pathway.

26. The method of claim 25, wherein the agent interacts with or regulates a component of the physiological pathway.

27. The method of claim 25, wherein the agent inhibits a physiologicalpathway.

28. The method of claim 25, wherein the agent enhances a physiologicalpathway.

29. The method of claim 25, wherein the physiological pathway is an insulin production pathway or a lipogenesis pathway.

30. A method for identifying a protein that regulates glucose metabolism, the method comprising the steps of:

a. measuring the expression in an isolated mRNP complex of at least one gene product of a cell involved in glucose metabolism, wherein the gene product is selected from the group consisting of an RNA binding protein, an mRNA associated with said RNA binding protein, or an mRNP complex-associated protein;

b. treating the cell with an agent selected from the group consisting of insulin, glucose, insulin-like growth factor-1 (IGF-1), a β-adrenergic agonist, glucose, glucagon-like peptide-1 (GLP-1), fatty acid, a peroxisome proliferator activated receptor (PPAR) ligand, and insulin-like growth factor 2 (IGF-2); and

c. measuring the expression of the gene product after treatment, wherein a difference in expression of the gene product after treatment compared to expression of the gene product before treatment is indicative that the protein regulates glucose metabolism.

31. A method for identifying an agent that regulates insulin production, the method comprising the steps of:

a. contacting a cell involves in insulin production with a nucleic acid capable of binding to at least one protein, wherein the protein is capable of binding to a 3' untranslated region or a 5' untranslated region of a preproinsulin mRNA;

b. separating the nucleic acid from the protein; and

c. identifying the protein.

32. The method of claim 31, wherein the protein binds to a nucleic acid comprising a sequence selected from the group consisting of 5'-gaauaaaaccuuugaaagagcacuac-3', 5'-cccaccacuacccuguccaccccucugcaaug-3', and 5'-agccctaagtgaccagctacagtcggaaaccatcagcaagcaggtcattgttccaac-3'.

33. An mRNP complex-associated with at least one of glucose or lipid metabolism, wherein the mRNP complex comprises a polypyrimidine tract binding (PTB) protein, and at least one mRNA associated with the polypyrimidine tract binding protein.

34. A method for identifying a component of an mRNP complex, the method comprising the steps of:

(a) transfecting a cell sample with a nucleic acid that inhibits the expression of an RNA binding protein;

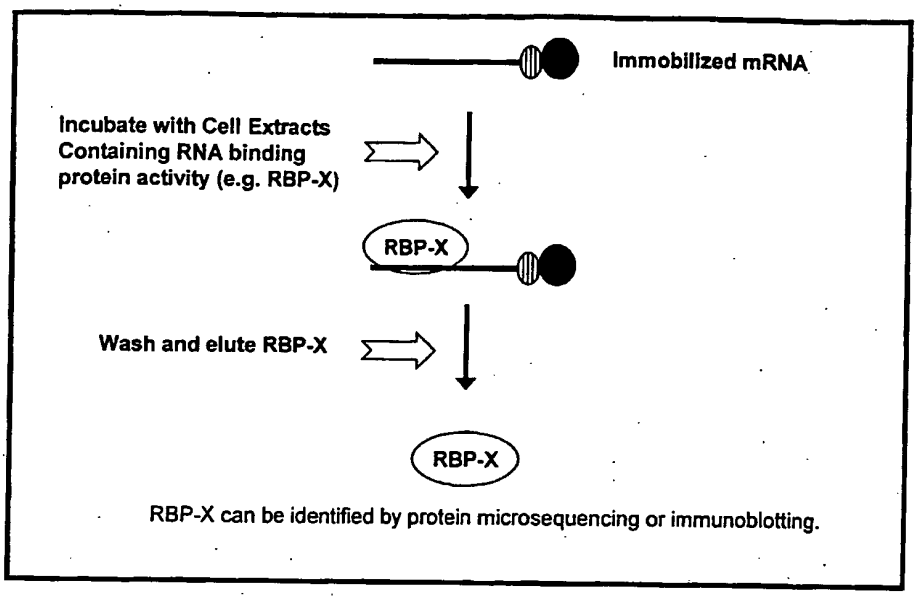
(b) isolating total RNA from the cell sample and from a control sample;

(c) identifying RNAs that have altered expression in the nucleic acid-transfected sample compared to the control sample.

35. The method of any one of claims 1, 7, 18, and 20, wherein the disease is related to aberrant glucose or lipid metabolism.

36. The method of claim 21 or 25, wherein the physiological pathway comprises a glucose or lipid metabolic pathway.

37. The method of any one of claims 1, 17, 20, 25, and 30, wherein at least one of said measuring and said comparing steps comprises the use of an array.



Biotinylated mRNA

Streptavidin-agarose support

RNA binding protein of interest RBP-X

Figure 1

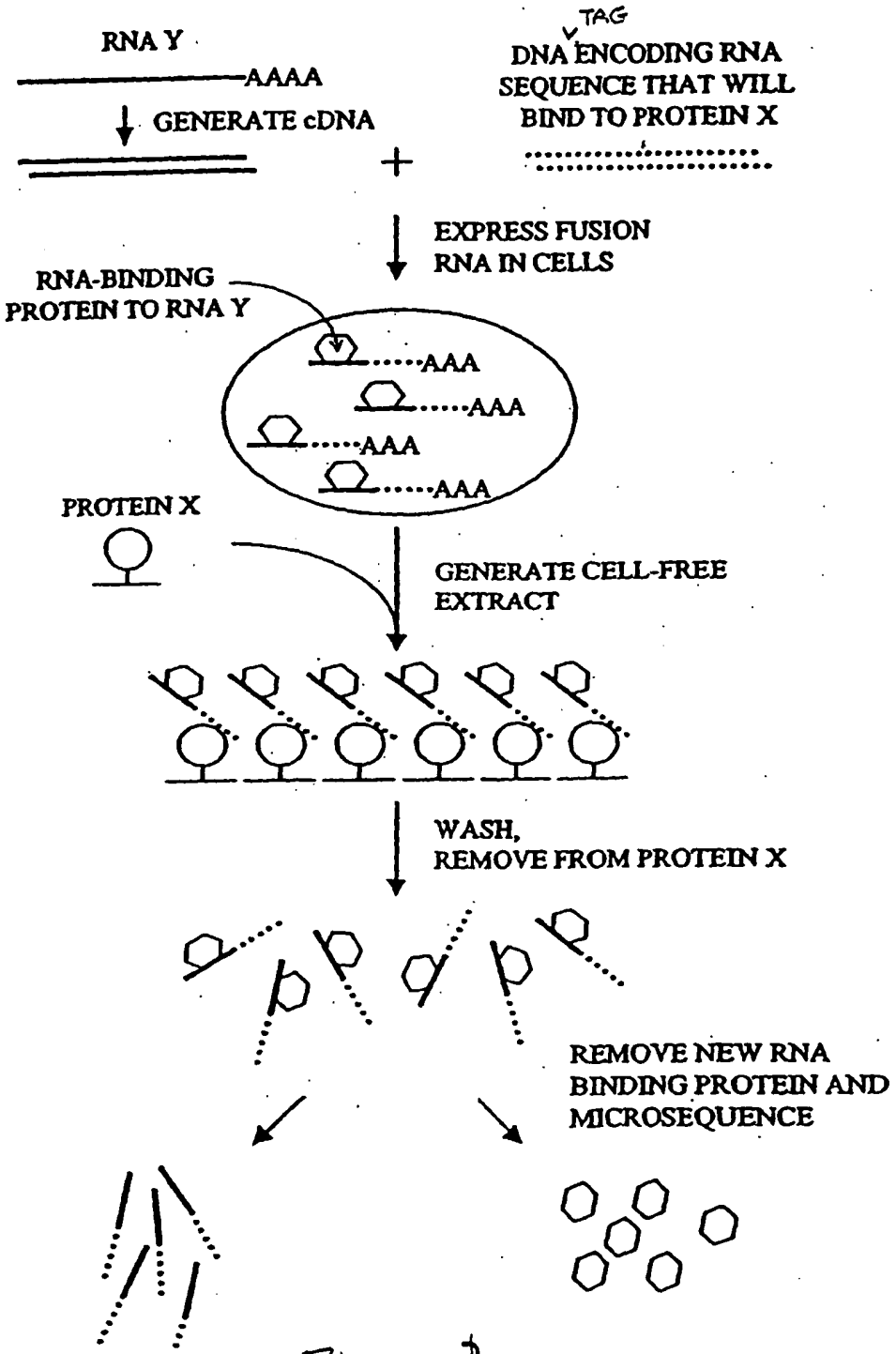

RNA Y
AAAA
GENERATE cDNA
TAG
DNA ENCODING RNA SEQUENCE THAT WILL BIND TO PROTEIN X
EXPRESS FUSION RNA IN CELLS
RNA-BINDING PROTEIN TO RNA Y
AAA
AAA
AAA
AAA
PROTEIN X
GENERATE CELL-FREE EXTRACT
WASH, REMOVE FROM PROTEIN X
REMOVE NEW RNA BINDING PROTEIN AND MICROSEQUENCE

Figure 2

Ribonome

The Ribonome is the entire collection of RNAs and their associated RNA binding proteins (RBPs).

Ribonomic Clusters

RAS™ segregates the ribonome into distinct ribonomic 'clusters' based upon a specific RBP. Genes within each cluster are identified by microarray.

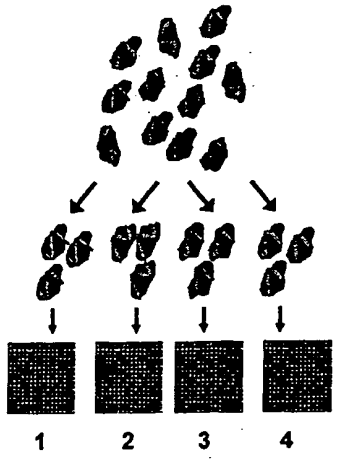


Figure 3

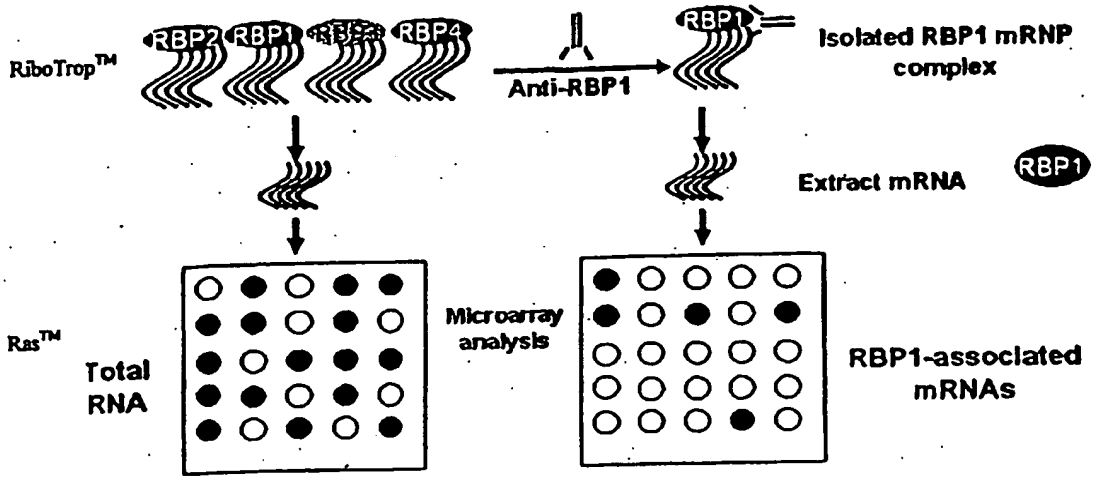

RiboTrop™
RBP2
RBP1
RBP3
RBP4
Anti-RBP1
RBP1
Isolated RBP1 mRNP complex
Extract mRNA
RBP1
Ras™
Total RNA
Microarray analysis
RBP1-associated mRNAs
•Global view of transcriptome
•Low sensitivity
•Complex Data Sets
•Enriched subset of mRNAs
•Higher Sensitivity
•Focus–Simplifies Data sets
•Many in same pathway, i.e. 'functionally related'
•Identify Novel Components

Figure 4

Expression of RNA Binding Protein Profile

↓

Production of Antibodies to RNA Binding Proteins

↓

Immunoprecipitation of mRNP Complexes

↓

Identification and Comparison of RNAs in mRNP Complexes

↓

Validation of the Biological Role of Genes Encoding RNAs of mRNP Complexes

Figure 5

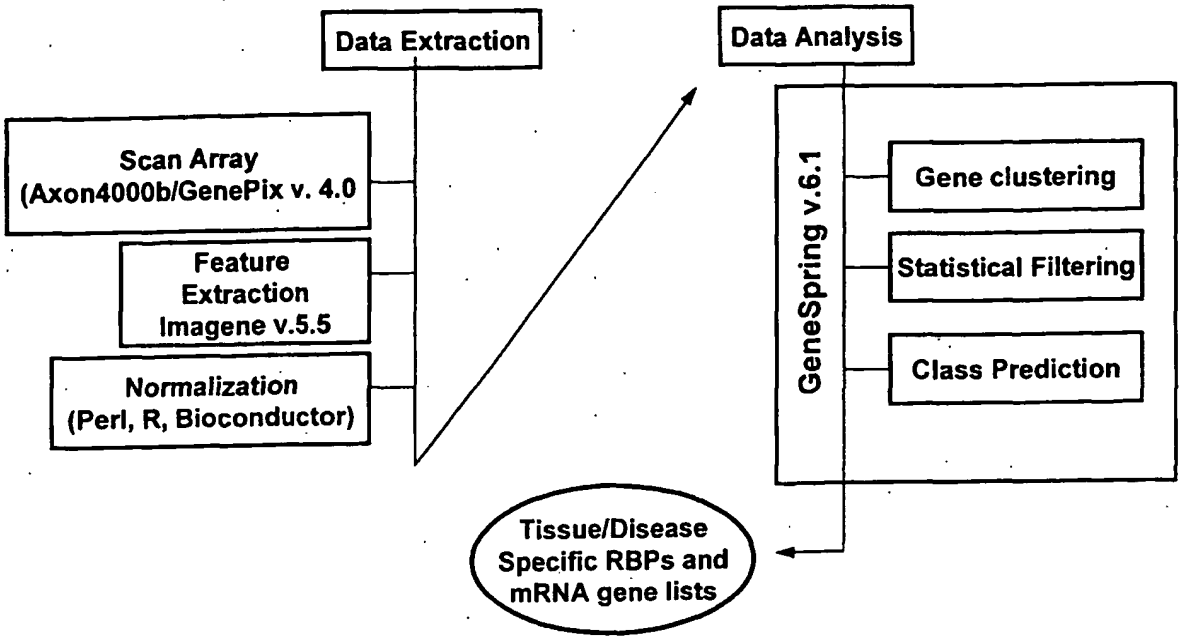

Data Extraction
Data Analysis
Scan Array
(Axon4000b/GenePix v. 4.0
Feature
Extraction
Imagene v.5.5
Normalization
(Perl, R, Bioconductor)
GeneSpring v.6.1
Gene clustering
Statistical Filtering
Class Prediction
Tissue/Disease
Specific RBPs and
mRNA gene lists

Figure 6

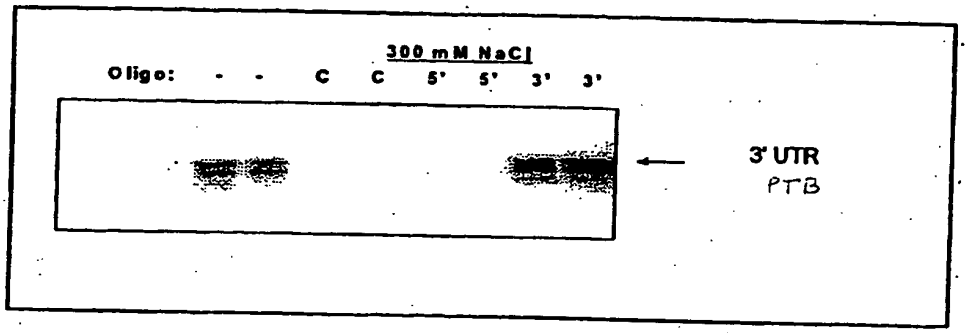
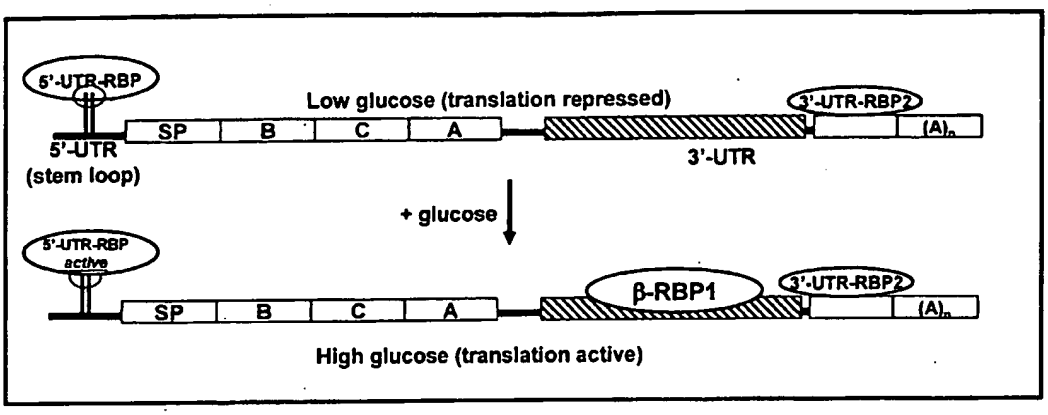


Figure 7



Model for binding of RBPs to preproinsulin mRNA

Figure 8

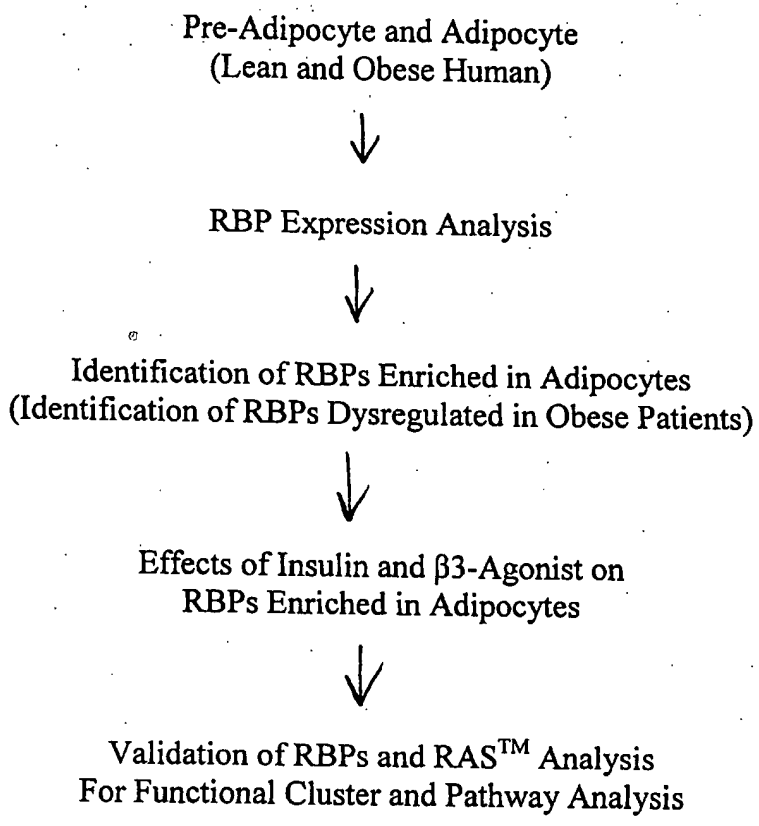

Pre-Adipocyte and Adipocyte
(Lean and Obese Human)
RBP Expression Analysis
Identification of RBPs Enriched in Adipocytes
(Identification of RBPs Dysregulated in Obese Patients)
Effects of Insulin and β3-Agonist on
RBPs Enriched in Adipocytes
Validation of RBPs and RAS™ Analysis
For Functional Cluster and Pathway Analysis

Figure 9

Nucleotide GenBank Accession Number or Manufacturer Sequence ID	Gene Name or Manufacturer Probe Name	Protein Product GeneBank Accsssion Number or Manufacturer Sequence Reference	Description
NM_006413	RPP30	NP_006404	Homo sapiens ribonuclease P/MRP 30kDa subunit (RPP30), mRNA.
NM_020967	NCOA5	NP_066018	Homo sapiens nuclear receptor coactivator 5 (NCOA5), mRNA.
NM_005058	RBMY1A1	NP_005049	Homo sapiens RNA binding motif protein, Y-linked, family 1, member A1 (RBMY1A1), mRNA.
NM_018380	DDX28	NP_060850	Homo sapiens DEAD (Asp-Glu-Ala-Asp) box polypeptide 28 (DDX28), nuclear gene encoding mitochondrial protein, mRNA.
NM_020158	RRP46	NP_064543	Homo sapiens exosome component Rrp46 (RRP46), mRNA.
XM_062047	LOC120470	XP_062047	Homo sapiens similar to discs, large (Drosophila) homolog 2; chapsyn-110 (LOC120470), mRNA.
NM_003429	ZNF85	NP_003420	Homo sapiens zinc finger protein 85 (HPF4, HTF1) (ZNF85), mRNA.
NM_005437	NCOA4	NP_005428	Homo sapiens nuclear receptor coactivator 4 (NCOA4), mRNA.
NM_000281	PCBD	NP_000272	Homo sapiens 6-pyruvoyl-tetrahydropterin synthase/dimerization cofactor of hepatocyte nuclear factor 1 alpha (TCF1) (PCBD), mRNA.
NM_022915	MRPL44	NP_075066	Homo sapiens mitochondrial ribosomal protein L44 (MRPL44), nuclear gene encoding mitochondrial protein, mRNA.
XM_068863	LOC134477	XP_068863	Homo sapiens similar to Hypothetical protein CGI-79 (LOC134477), mRNA.
AK000256		BAA91036	Homo sapiens cDNA FLJ20249 fis, clone COLF6621.
NM_002197	ACO1	NP_002188	Homo sapiens aconitase 1, soluble (ACO1), mRNA.
XM_066446	LOC139051	XP_066446	Homo sapiens similar to pol protein (LOC139051), mRNA.
NM_000989	RPL30	NP_000980	Homo sapiens ribosomal protein L30 (RPL30), mRNA.
NM_005119	THRAP3	NP_005110	Homo sapiens thyroid hormone receptor associated protein 3 (THRAP3), mRNA.
AF254411	SR-A1	AAF87552	Homo sapiens ser/arg-rich pre-mRNA splicing factor SR-A1 (SR-A1) gene, complete cds.
NM_006311	NCOR1	NP_006302	Homo sapiens nuclear receptor co-repressor 1 (NCOR1), mRNA.
M58511	IRE-BP2/IRP2	AAA69901	Human iron-responsive element-binding protein/iron regulatory protein 2 (IRE-BP2/IRP2) mRNA, partial cds.

FIGURE 10

Nucleotide GenBank Accession Number or Manufacturer Sequence ID	Gene Name or Manufacturer Probe Name	Protein Product GeneBank Accsssion Number or Manufacturer Sequence Reference	Description
XM_065361	LOC129715	XP_065361	Homo sapiens similar to tudor protein (LOC129715), mRNA.
NM_019038	TDRD4	NP_061911	Homo sapiens tudor domain containing 4 (TDRD4), mRNA.
NM_022768	RBM15	NP_073605	Homo sapiens RNA binding motif protein 15 (RBM15), mRNA.
NM_000077	CDKN2A	NP_000068	Homo sapiens cyclin-dependent kinase inhibitor 2A (melanoma, p16, inhibits CDK4) (CDKN2A), transcript variant 1, mRNA.
AB011167	KIAA0595	BAA25521	Homo sapiens mRNA for KIAA0595 protein, partial cds.
NM_022360	FAM12B	NP_071755	Homo sapiens family with sequence similarity 12, member B (epididymal) (FAM12B), mRNA.
XM_091042	LOC161682	XP_091042	Homo sapiens similar to data source:MGD, source key:MGI:107795, evidence:ISS~heterogeneous nuclear ribonucleoprotein C~putative (LOC161682), mRNA.
XM_089062	LOC148866	XP_089062	Homo sapiens similar to HETEROGENEOUS NUCLEAR RIBONUCLEOPROTEIN A1 (HELIX-DESTABILIZING PROTEIN) (SINGLE-STRAND BINDING PROTEIN) (HNRNP CORE PROTEIN A1) (LOC148866), mRNA.
XM_063247	LOC122648	XP_063247	Homo sapiens similar to putative pancreatic ribonuclease (LOC122648), mRNA.
XM_061549	LOC119579	XP_061549	Homo sapiens LOC119579 (LOC119579), mRNA.
NM_016200	LSM8	NP_057284	Homo sapiens LSM8 homolog, U6 small nuclear RNA associated (S. cerevisiae) (LSM8), mRNA.
NM_017993	FLJ10094	NP_060463	Homo sapiens hypothetical protein FLJ10094 (FLJ10094), mRNA.
XM_061319	LOC119177	XP_061319	Homo sapiens similar to HETEROGENEOUS NUCLEAR RIBONUCLEOPROTEIN A1 (HELIX-DESTABILIZING PROTEIN) (SINGLE-STRAND BINDING PROTEIN) (HNRNP CORE PROTEIN A1) (LOC119177), mRNA.
NM_007372	DDX42	NP_031398	Homo sapiens DEAD (Asp-Glu-Ala-Asp) box polypeptide 42 (DDX42), transcript variant 1, mRNA.
XM_092489	LOC165271	XP_092489	Homo sapiens similar to heterogeneous nuclear ribonucleoprotein K (LOC165271), mRNA.
NM_000967	RPL3	NP_000958	Homo sapiens ribosomal protein L3 (RPL3), mRNA.
NM_033117	RBM18	NP_149108	Homo sapiens RNA binding motif protein 18 (RBM18), mRNA.
AF285599	STK31	AAK31978	Homo sapiens serine/threonine kinase 31 (STK31) mRNA, complete cds.
NM_007363	NONO	NP_031389	Homo sapiens non-POU domain containing, octamer-binding (NONO), mRNA.
NM_002939	RNH	NP_002930	Homo sapiens ribonuclease/angiogenin inhibitor (RNH), transcript variant 1, mRNA.

Figure 10

Nucleotide GenBank Accession Number or Manufacturer Sequence ID	Gene Name or Manufacturer Probe Name	Protein Product GeneBank Accsssion Number or Manufacturer Sequence Reference	Description
XM_066901	LOC139801	XP_066901	Homo sapiens LOC139801 (LOC139801), mRNA.
NM_006074	TRIM22	NP_006065	Homo sapiens tripartite motif-containing 22 (TRIM22), mRNA.
XM_070605	LOC137786	XP_070605	Homo sapiens similar to ANTIGEN GOR (LOC137786), mRNA.
XM_090917	LOC161461	XP_090917	Homo sapiens LOC161461 (LOC161461), mRNA.
XM_093219	LOC170270	XP_093219	Homo sapiens similar to Heterogeneous nuclear ribonucleoprotein A3 homolog 2 (hnRNP A3(B)) (LOC170270), mRNA.
NM_004294	MTRF1	NP_004285	Homo sapiens mitochondrial translational release factor 1 (MTRF1), nuclear gene encoding mitochondrial protein, mRNA
NM_001605	AARS	NP_001596	Homo sapiens alanyl-tRNA synthetase (AARS), mRNA.
XM_068154	LOC133037	XP_068154	Homo sapiens LOC133037 (LOC133037), mRNA.
XM_094140	LOC166863	XP_094140	Homo sapiens similar to Apobec-1 complementation factor, APOBEC-1 stimulating protein (LOC166863), mRNA.
X99302	pop1	CAA67684	H.sapiens mRNA for Pop1 protein.
XM_066606	LOC139272	XP_066606	Homo sapiens similar to eukaryotic initiation factor 4B (LOC139272), mRNA.

Figure 10

Nucleotide GenBank Accession Number or Manufacturer Sequence ID	Gene Name or Manufacturer Probe Name	Protein Product GeneBank Accsssion Number or Manufacturer Sequence Reference	Description
XM_070830	LOC138280	XP_070830	Homo sapiens similar to KIAA1138 protein (LOC138280), mRNA.
XM_092489	LOC165271	XP_092489	Homo sapiens similar to heterogeneous nuclear ribonucleoprotein K (LOC165271), mRNA.
NM_006413	RPP30	NP_006404	Homo sapiens ribonuclease P/MRP 30kDa subunit (RPP30), mRNA.
NM_002934	RNASE2	NP_002925	Homo sapiens ribonuclease, RNase A family, 2 (liver, eosinophil-derived neurotoxin) (RNASE2), mRNA.
NM_005058	RBMY1A1	NP_005049	Homo sapiens RNA binding motif protein, Y-linked, family 1, member A1 (RBMY1A1), mRNA.
NM_022360	FAM12B	NP_071755	Homo sapiens family with sequence similarity 12, member B (epididymal) (FAM12B), mRNA.
XM_065361	LOC129715	XP_065361	Homo sapiens similar to tudor protein (LOC129715), mRNA.
NM_020967	NCOA5	NP_066018	Homo sapiens nuclear receptor coactivator 5 (NCOA5), mRNA.
NM_001024	RPS21	NP_001015	Homo sapiens ribosomal protein S21 (RPS21), mRNA.
NM_006187	OAS3	NP_006178	Homo sapiens 2'-5'-oligoadenylate synthetase 3, 100kDa (OAS3), mRNA.
NM_031994	RNF17	NP_114383	Homo sapiens ring finger protein 17 (RNF17), transcript variant short, mRNA.
XM_060358	LOC127164	XP_060358	Homo sapiens similar to TAR DNA binding protein (LOC127164), mRNA.
NM_002534	OAS1	NP_002525	Homo sapiens 2',5'-oligoadenylate synthetase 1, 40/46kDa (OAS1), transcript variant E16, mRNA.
NM_018380	DDX28	NP_060850	Homo sapiens DEAD (Asp-Glu-Ala-Asp) box polypeptide 28 (DDX28), nuclear gene encoding mitochondrial protein, mRNA.

Figure 11

Nucleotide GenBank Accession Number or Manufacturer Sequence ID	Gene Name or Manufacturer Probe Name	Protein Product GeneBank Accsssion Number or Manufacturer Sequence Reference	Description
NM_025134	FLJ12178	NP_079410	Homo sapiens hypothetical protein FLJ12178 (FLJ12178), mRNA.
XM_065361	LOC129715	XP_065361	Homo sapiens similar to tudor protein (LOC129715), mRNA.
NM_004768	SFRS11	NP_004759	Homo sapiens splicing factor, arginine/serine-rich 11 (SFRS11), mRNA.
XM_066446	LOC139051	XP_066446	Homo sapiens similar to pol protein (LOC139051), mRNA.
NM_004592	SFRS8	NP_004583	Homo sapiens splicing factor, arginine/serine-rich 8 (suppressor-of-white-apricot homolog, Drosophila) (SFRS8), transcript variant 2A, mRNA.
XM_069688	LOC136068	XP_069688	Homo sapiens LOC136068 (LOC136068), mRNA.
NM_022830	FLJ22347	NP_073741	Homo sapiens hypothetical protein FLJ22347 (FLJ22347), mRNA.
NM_013235	RNASE3L	NP_037367	Homo sapiens nuclear RNase III Drosha (RNASE3L), mRNA.
NM_003758	EIF3S1	NP_003749	Homo sapiens eukaryotic translation initiation factor 3, subunit 1 alpha, 35kDa (EIF3S1), mRNA.
NM_005381	NCL	NP_005372	Homo sapiens nucleolin (NCL), mRNA.
NM_001145	ANG	NP_001136	Homo sapiens angiogenin, ribonuclease, RNase A family, 5 (ANG), mRNA.
XM_067085	LOC140121	XP_067085	Homo sapiens similar to Heterogeneous nuclear ribonucleoprotein G (hnRNP G) (RNA binding motif protein, X chromosome) (LOC140121), mRNA.
XM_012968	LOC151921	XP_012968	Homo sapiens similar to chromosome 20 open reading frame 14; putative mitochondrial outer membrane protein import receptor; similar to yeast pre-mRNA splicing factors, Prp1/Zer and Prp6 (LOC151921), mRNA.
NM_006170	NOL1	NP_006161	Homo sapiens nucleolar protein 1, 120kDa (NOL1), mRNA.
NM_005617	RPS14	NP_005608	Homo sapiens ribosomal protein S14 (RPS14), mRNA.

Figure 12

Nucleotide GenBank Accession Number or Manufacturer Sequence ID	Gene Name or Manufacturer Probe Name	Protein Product GeneBank Accsssion Number or Manufacturer Sequence Reference	Description
NM_006546	IMP-1	NP_006537	Homo sapiens IGF-II mRNA-binding protein 1 (IMP-1), mRNA.
NM_004689	MTA1	NP_004680	Homo sapiens metastasis associated 1 (MTA1), mRNA.
NM_020143	LOC56902	NP_064528	Homo sapiens putatative 28 kDa protein (LOC56902), mRNA.
NM_003096	SNRPG	NP_003087	Homo sapiens small nuclear ribonucleoprotein polypeptide G (SNRPG), mRNA.
NM_000947	PRIM2A	NP_000938	Homo sapiens primase, polypeptide 2A, 58kDa (PRIM2A), mRNA.
NM_006312	NCOR2	NP_006303	Homo sapiens nuclear receptor co-repressor 2 (NCOR2), mRNA.

Figure 12

Nucleotide GenBank Accession Number or Manufacturer Sequence ID	Gene Name or Manufacturer Probe Name	Protein Product GeneBank Accsssion Number or Manufacturer Sequence Reference	Description
NM_006312	NCOR2	NP_006303	Homo sapiens nuclear receptor co-repressor 2 (NCOR2), mRNA.
NM_006546	IMP-1	NP_006537	Homo sapiens IGF-II mRNA-binding protein 1 (IMP-1), mRNA.
NM_020143	LOC56902	NP_064528	Homo sapiens putatative 28 kDa protein (LOC56902), mRNA.
XM_047499	LOC149603	XP_047499	Homo sapiens hypothetical protein LOC149603 (LOC149603), mRNA.
NM_018415	TRERF1	NP_060885	Homo sapiens transcriptional regulating factor 1 (TRERF1), transcript variant 3, mRNA.
NM_000947	PRIM2A	NP_000938	Homo sapiens primase, polypeptide 2A, 58kDa (PRIM2A), mRNA.
NM_013264	DDX25	NP_037396	Homo sapiens DEAD (Asp-Glu-Ala-Asp) box polypeptide 25 (DDX25), mRNA.
XM_095071	CAGE	XP_095071	Homo sapiens cancer-associated gene (CAGE), mRNA.
U23028		AAC50646	Human eukaryotic initiation factor 2B-epsilon mRNA, partial cds.
NM_015891	CDC40	NP_056975	Homo sapiens cell division cycle 40 homolog (yeast) (CDC40), mRNA.
NM_015453	DKFZP434F091	NP_056268	Homo sapiens DKFZP434F091 protein (DKFZP434F091), mRNA.
NM_030794	TDRD3	NP_110421	Homo sapiens tudor domain containing 3 (TDRD3), mRNA.
AF049523	HYPA	AAC27501	Homo sapiens huntingtin-interacting protein HYPA/FBP11 (HYPA) mRNA, partial cds.
XM_088868	LOC163412	XP_088868	Homo sapiens LOC163412 (LOC163412), mRNA.
NM_033030	BOLL	NP_149019	Homo sapiens bol, boule-like (Drosophila) (BOLL), transcript variant 2, mRNA.
NM_022915	MRPL44	NP_075066	Homo sapiens mitochondrial ribosomal protein L44 (MRPL44), nuclear gene encoding mitochondrial protein mRNA.
XM_087251	FLJ00166	XP_087251	Homo sapiens FLJ00166 protein (FLJ00166), mRNA.
NM_003096	SNRPG	NP_003087	Homo sapiens small nuclear ribonucleoprotein polypeptide G (SNRPG), mRNA.
NM_004937	CTNS	NP_004928	Homo sapiens cystinosis, nephropathic (CTNS), mRNA.
NM_004689	MTA1	NP_004680	Homo sapiens metastasis associated 1 (MTA1), mRNA.
AF026126	HNRPD	AAC23476	Homo sapiens heterogeneous nuclear ribonucleoprotein D (HNRPD) gene, complete cds.
NM_002502	NFKB2	NP_002493	Homo sapiens nuclear factor of kappa light polypeptide gene enhancer in B-cells 2 (p49/p100) (NFKB2), mRNA.
AF254411	SR-A1	AAF87552	Homo sapiens ser/arg-rich pre-mRNA splicing factor SR-A1 (SR-A1) gene, complete cds.

Figure 13

Nucleotide GenBank Accession Number or Manufacturer Sequence ID	Gene Name or Manufacturer Probe Name	Protein Product GeneBank Accsssion Number or Manufacturer Sequence Reference	Description
XM_064989	LOC126205	XP_064989	Homo sapiens similar to PYRIN-containing APAF1-like protein 7; PYRIN-containing APAF1-like protein mRNA; monarch 1 [Homo sapiens] (LOC126205), mRNA.
XM_070263	LOC137165	XP_070263	Homo sapiens similar to ribosomal protein L3; 60S ribosomal protein L3; HIV-1 TAR RNA-binding protein B (LOC137165), mRNA.
NM_006388	HTATIP	NP_006379	Homo sapiens HIV-1 Tat interactive protein, 60kDa (HTATIP), transcript variant 2, mRNA.
NM_006209	ENPP2	NP_006200	Homo sapiens ectonucleotide pyrophosphatase/phosphodiesterase 2 (autotaxin) (ENPP2), mRNA.
BC012090		AAH12090	Homo sapiens, Similar to heterogeneous nuclear ribonucleoprotein A3, clone MGC:20045 IMAGE:4661041 mRNA, complete cds.
NM_001019	RPS15A	NP_001010	Homo sapiens ribosomal protein S15a (RPS15A), mRNA.
NM_021133	RNASEL	NP_066956	Homo sapiens ribonuclease L (2',5'-oligoisoadenylate synthetase-dependent) (RNASEL), mRNA.
NM_013235	RNASE3L	NP_037367	Homo sapiens nuclear RNase III Drosha (RNASE3L), mRNA.
NM_015235	CSTF2T	NP_056050	Homo sapiens cleavage stimulation factor, 3' pre-RNA, subunit 2, 64kDa, tau variant (CSTF2T), mRNA.
NM_004094	EIF2S1	NP_004085	Homo sapiens eukaryotic translation initiation factor 2, subunit 1 alpha, 35kDa (EIF2S1), mRNA.
NM_006163	NFE2	NP_006154	Homo sapiens nuclear factor (erythroid-derived 2), 45kDa (NFE2), mRNA.
NM_014003	DHX38	NP_054722	Homo sapiens DEAH (Asp-Glu-Ala-His) box polypeptide 38 (DHX38), mRNA.
NM_006789	APOBEC2	NP_006780	Homo sapiens apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 2 (APOBEC2), mRNA.
NM_014285	RRP4	NP_055100	Homo sapiens homolog of Yeast RRP4 (ribosomal RNA processing 4), 3'-5'-exoribonuclease (RRP4), mRNA.
NM_004175	SNRPD3	NP_004166	Homo sapiens small nuclear ribonucleoprotein D3 polypeptide 18kDa (SNRPD3), mRNA.
AL117473	DKFZp727A071	CAB55948	Homo sapiens mRNA; cDNA DKFZp727A071 (from clone DKFZp727A071); partial cds.
XM_085059	LOC145223	XP_085059	Homo sapiens similar to Splicing factor 3B subunit 4 (Spliceosome associated protein 49) (SAP 49) (SF3b5 (Pre-mRNA splicing factor SF3b 49 kDa subunit) (LOC145223), mRNA.

Figure 13

Nucleotide GenBank Accession Number or Manufacturer Sequence ID	Gene Name or Manufacturer Probe Name	Protein Product GeneBank Accsssion Number or Manufacturer Sequence Reference	Description
NM_020158	RRP46	NP_064543	Homo sapiens exosome component Rrp46 (RRP46), mRNA.
NM_016024	CGI-79	NP_057108	Homo sapiens CGI-79 protein (CGI-79), mRNA.
XM_065361	LOC129715	XP_065361	Homo sapiens similar to tudor protein (LOC129715), mRNA.
XM_068863	LOC134477	XP_068863	Homo sapiens similar to Hypothetical protein CGI-79 (LOC134477), mRNA.
NM_006527	SLBP	NP_006518	Homo sapiens stem-loop (histone) binding protein (SLBP), mRNA.
NM_024321	MGC10433	NP_077297	Homo sapiens hypothetical protein MGC10433 (MGC10433), mRNA.
NM_003075	SMARCC2	NP_003066	Homo sapiens SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily c, member 2 (SMARCC2), transcript variant 1, mRNA.
NM_016955	SLA/LP	NP_058651	Homo sapiens soluble liver antigen/liver pancreas antigen (SLA/LP), mRNA.
NM_002819	PTBP1	NP_002810	Homo sapiens polypyrimidine tract binding protein 1 (PTBP1), transcript variant 1, mRNA.
NM_001021	RPS17	NP_001012	Homo sapiens ribosomal protein S17 (RPS17), mRNA.
NM_002568	PABPC1	NP_002559	Homo sapiens poly(A) binding protein, cytoplasmic 1 (PABPC1), mRNA.
NM_014871	USP52	NP_055686	Homo sapiens ubiquitin specific protease 52 (USP52), mRNA.
NM_003076	SMARCD1	NP_003067	Homo sapiens SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily d, member 1 (SMARCD1), transcript variant 1, mRNA.
NM_006547	IMP-3	NP_006538	Homo sapiens IGF-II mRNA-binding protein 3 (IMP-3), mRNA.
NM_025134	FLJ12178	NP_079410	Homo sapiens hypothetical protein FLJ12178 (FLJ12178), mRNA.
NM_002695	POLR2E	NP_002686	Homo sapiens polymerase (RNA) II (DNA directed) polypeptide E, 25kDa (POLR2E), mRNA.
NM_005801	SUI1	NP_005792	Homo sapiens putative translation initiation factor (SUI1), mRNA.
NM_022830	FLJ22347	NP_073741	Homo sapiens hypothetical protein FLJ22347 (FLJ22347), mRNA.
NM_012245	SNW1	NP_036377	Homo sapiens SKI-interacting protein (SNW1), mRNA.
NM_005617	RPS14	NP_005608	Homo sapiens ribosomal protein S14 (RPS14), mRNA.
NM_021134	MRPL23	NP_066957	Homo sapiens mitochondrial ribosomal protein L23 (MRPL23), nuclear gene encoding mitochondrial protein mRNA.

Figure 13

XM_058421	LOC119832	XP_058421	Homo sapiens similar to HETEROGENEOUS NUCLEAR RIBONUCLEOPROTEIN A1 (HELIX-DESTABILIZING PROTEIN) (SINGLE-STRAND BINDING PROTEIN) (HNRNP CORE PROTEIN A1) (LOC119832), mRNA.
NM_006013	RPL10	NP_006004	Homo sapiens ribosomal protein L10 (RPL10), mRNA.

Figure 13

Nucleotide GenBank Accession Number or Manufacturer Sequence ID	Gene Name or Manufacturer Probe Name	Protein Product GeneBank Accsssion Number or Manufacturer Sequence Reference	Description
XM_085111	LOC145359		Homo sapiens similar to RIBONUCLEASE PANCREATIC PRECURSOR (RNASE 1) (RNASE A) (LOC145359), mRNA.
XM_047920	LOC92906		Homo sapiens similar to Unknown (protein for IMAGE:3587716) (LOC92906), mRNA.
XM_060628	LOC127722		Homo sapiens similar to HETEROGENEOUS NUCLEAR RIBONUCLEOPROTEIN A1 (HELIX-DESTABILIZING PROTEIN) (SINGLE-STRAND BINDING PROTEIN) (HNRNP CORE PROTEIN A1) (UNWINDING PROTEIN 1) (UP1) (LOC127722), mRNA.
XM_088640	LOC158685		Homo sapiens similar to RNA-binding region (RNP1, RRM) containing 2 (H. sapiens) (LOC158685), mRNA.
XM_017931	LOC158201		Homo sapiens similar to RNA binding motif protein, X chromosome (H. sapiens) (LOC158201), mRNA.
XM_062047	LOC120470		Homo sapiens similar to discs, large (Drosophila) homolog 2; chapsyn-110 (LOC120470), mRNA.
XM_068997	LOC134759		Homo sapiens similar to heterogeneous nuclear ribonucleoprotein L (LOC134759), mRNA.
XM_087697	LOC153522		Homo sapiens similar to splicing factor, arginine/serine-rich 11 (LOC153522), mRNA.
NM_003191	TARS		Homo sapiens threonyl-tRNA synthetase (TARS), mRNA.
XM_061850	LOC120083		Homo sapiens similar to 46kD arginine/serine-rich splicing factor (LOC120083), mRNA.
XM_093219	LOC170270		Homo sapiens similar to HETEROGENEOUS NUCLEAR RIBONUCLEOPROTEIN A3 HOMOLOG 2 (HNRNP A3(B)) (LOC170270), mRNA.
XM_068457	LOC133655		Homo sapiens similar to splicing coactivator subunit SRm300; RNA binding protein; AT-rich element binding factor; serine/arginine repetitive matrix 2 (LOC133655), mRNA.
NM_014892	KIAA1116		Homo sapiens KIAA1116 protein (KIAA1116), mRNA.
XM_058819	LOC124540		Homo sapiens similar to RNA-binding protein Musashi2-S (LOC124540), mRNA.
XM_058653	LOC122651		Homo sapiens similar to RIBONUCLEASE PANCREATIC (RNASE 1) (RNASE A) (LOC122651), mRNA.
XM_093626	LOC152108		Homo sapiens similar to ubiquitin A-52 residue ribosomal protein fusion product 1 (LOC152108), mRNA.
XM_061002	LOC118523		Homo sapiens similar to SON DNA binding protein; SON DNA-binding protein; SON DNA-binding protein, KIAA1019; NRE-binding protein (H. sapiens) (LOC118523), mRNA.
XM_060358	LOC127164		Homo sapiens similar to TAR DNA binding protein (LOC127164), mRNA.

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Nucleotide GenBank Accession Number or Manufacturer Sequence ID	Gene Name or Manufacturer Probe Name	Protein Product GeneBank Accession Number or Manufacturer Sequence Reference	Description
XM_063601	LOC123341		Homo sapiens similar to HETEROGENEOUS NUCLEAR RIBONUCLEOPROTEIN A1 (HELIX-DESTABILIZING PROTEIN) (SINGLE-STRAND BINDING PROTEIN) (HNRNP CORE PROTEIN A1) (UNWINDING PROTEIN 1) (UP1) (LOC123341), mRNA.
XM_059612	LOC132928		Homo sapiens similar to poly(A) binding protein, cytoplasmic 1; poly(A)-binding protein, cytoplasmic 1 (LOC132928), mRNA
NM_021993	FUSIP1		Homo sapiens FUS interacting protein (serine-arginine rich) 1 (FUSIP1) transcript variant 2, mRNA.
XM_064113	LOC124380		Homo sapiens similar to Hrb27C-P1; RNA-binding protein 7 (LOC124380), mRNA.
XM_098297	LOC153028		Homo sapiens similar to RNA binding protein S1, serine-rich domain (H. sapiens) (LOC153028), mRNA.
XM_062934	LOC122056		Homo sapiens similar to ATP-DEPENDENT RNA HELICASE A (NUCLEAR DNA HELICASE II) (NDH II) (DEAD-BOX PROTEIN 9) (LOC122056), mRNA.
XM_053153	LOC149973		Homo sapiens similar to RNA binding motif protein, X chromosome (H. sapiens) (LOC149973), mRNA.
XM_070603	LOC137784		Homo sapiens similar to ANTIGEN GOR (LOC137784), mRNA.
XM_086419	LOC149092		Homo sapiens similar to pumilio homolog 1 (Drosophila) (H. sapiens) (LOC149092), mRNA.
XM_067918	LOC132583		Homo sapiens similar to HETEROGENEOUS NUCLEAR RIBONUCLEOPROTEIN A1 (HELIX-DESTABILIZING PROTEIN) (SINGLE-STRAND BINDING PROTEIN) (HNRNP CORE PROTEIN A1) (LOC132583), mRNA.
NM_006450	SPF45		Homo sapiens splicing factor (45kD) (SPF45), mRNA.
NM_004940	DDX7		Homo sapiens DEAD/H (Asp-Glu-Ala-Asp/His) box polypeptide 7 (RNA helicase, 52kD) (DDX7), mRNA.
XM_086011	LOC148027		Homo sapiens similar to bruno-like 5, RNA binding protein (Drosophila); Bruno (Drosophila) -like 5, RNA binding protein CUG-BP and ETR-3 like factor 5; RNA-binding protein BRUNOL-5 (LOC148027), mRNA.
XM_073386	LOC119594		Homo sapiens similar to SPLICING FACTOR U2AF 65 KDA SUBUNIT (U2 AUXILIARY FACTOR 65 KDA SUBUNIT) (U2 SNRNP AUXILIARY FACTOR LARGE SUBUNIT) (U2AF65) (LOC119594), mRNA.
XM_067051	LOC140065		Homo sapiens similar to RNA binding motif protein, Y chromosome, family 1, member A1; RNA binding motif protein 1; RNA binding motif protein 2 (LOC140065), mRNA.
NM_003138	SRPK2		Homo sapiens SFRS protein kinase 2 (SRPK2), mRNA.
XM_092386	LOC165115		Homo sapiens similar to KIAA1841 protein (LOC165115), mRNA.

Nucleotide GenBank Accession Number or Manufacturer Sequence ID	Gene Name or Manufacturer Probe Name	Protein Product GeneBank Accsssion Number or Manufacturer Sequence Reference	Description
XM_062047	LOC120470		Homo sapiens similar to discs, large (Drosophila) homolog 2; chapsyn-110 (LOC120470), mRNA.
XM_092031	LOC163147		Homo sapiens similar to splicing factor 3a, subunit 2, 66kD; Spliceosome protein SAP-62 (LOC163147), mRNA.
XM_067074	LOC140100		Homo sapiens similar to RNA binding motif protein, Y chromosome, family 1, member A1; RNA binding motif protein; RNA binding motif protein 2 (LOC140100), mRNA.
XM_060102	LOC126635		Homo sapiens similar to splicing factor, arginine/serine-rich 2, interacting protein; SC35-interacting protein 1 (LOC126635), mRNA.
XM_001524	LOC151173		Homo sapiens similar to TAR DNA binding protein (H. sapiens) (LOC151173), mRNA.
XM_086792	LOC150152		Homo sapiens similar to SPLICING FACTOR U2AF 35 KD SUBUNIT (U2 AUXILIARY FACTOR 35 KD SUBUNIT) (U2 SNRNP AUXILIARY FACTOR SMALL SUBUNIT) (LOC150152), mRNA.
XM_070605	LOC137786		Homo sapiens similar to ANTIGEN GOR (LOC137786), mRNA.
NM_006842	SF3B2		Homo sapiens splicing factor 3b, subunit 2, 145kD (SF3B2), mRNA.
XM_095899	LOC169732		Homo sapiens similar to EXOSOME COMPLEX EXONUCLEASE RRP4 (RIBOSOMAL RNA PROCESSING PROTEIN 4) (LOC169732), mRNA.
XM_066446	LOC139051		Homo sapiens similar to hypothetical protein (LOC139051), mRNA.
XM_089765	LOC143344		Homo sapiens similar to poly(A) binding protein (LOC143344), mRNA.
XM_089587	LOC159428		Homo sapiens similar to EUKARYOTIC TRANSLATION INITIATION FACTOR 4B (EIF-4B) (LOC159428), mRNA.
XM_092043	LOC163160		Homo sapiens similar to polypyrimidine tract binding protein, isoform b; heterogeneous nuclear ribonucleoprotein polypeptic I; RNA binding protein (LOC163160), mRNA.
XM_091270	LOC161983		Homo sapiens similar to HETEROGENEOUS NUCLEAR RIBONUCLEOPROTEIN A1 (HELIX-DESTABILIZING PROTEIN) (SINGLE-STRAND BINDING PROTEIN) (HNRNP CORE PROTEIN A1) (LOC161983), mRNA.
XM_067072	LOC140098		Homo sapiens similar to RBM1 (LOC140098), mRNA.
XM_056568	LOC147774		Homo sapiens similar to KH-type splicing regulatory protein (FUSE binding protein 2) (H. sapiens) (LOC147774), mRNA.

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Nucleotide GenBank Accession Number or Manufacturer Sequence ID	Gene Name or Manufacturer Probe Name	Protein Product GeneBank Accsssion Number or Manufacturer Sequence Reference	Description
XM_091235	LOC161931		Homo sapiens similar to hypothetical protein (LOC161931), mRNA.
XM_058943	LOC125925		Homo sapiens similar to R32611_1 (LOC125925), mRNA.
XM_058876	LOC124944		Homo sapiens similar to putative (H. sapiens) (LOC124944), mRNA.
XM_088975	LOC148683		Homo sapiens similar to pumilio homolog 1 (Drosophila); pumilio (Drosophila) homolog 1 (LOC148683), mRNA.
XM_092221	LOC164891		Homo sapiens similar to mRNA for ribosomal protein S9 (LOC164891), mRNA.
XM_095591	LOC169242		Homo sapiens similar to putative (LOC169242), mRNA.
XM_093336	LOC165631		Homo sapiens similar to KIAA1268 protein (LOC165631), mRNA.
XM_065002	LOC126246		Homo sapiens similar to Similar to splicing factor proline/glutamine rich (polypyrimidine tract-binding protein-associated) (H. sapiens) (LOC126246), mRNA.
XM_067452	LOC131596		Homo sapiens similar to splicing factor 3a, subunit 2, 66kD; Spliceosome protein SAP-62 (LOC131596), mRNA.
XM_062601	LOC121365		Homo sapiens similar to RBM1 (LOC121365), mRNA.
XM_068248	LOC133225		Homo sapiens similar to HETEROGENEOUS NUCLEAR RIBONUCLEOPROTEIN A1 (HELIX-DESTABILIZING PROTEIN) (SINGLE-STRAND BINDING PROTEIN) (HNRNP CORE PROTEIN A1) (H. sapiens) (LOC133225), mRNA.
XM_068022	LOC132772		Homo sapiens similar to split ends; polycephalon; yippee interacting protein 1 (LOC132772), mRNA.
XM_066901	LOC139801		Homo sapiens similar to splicing factor, arginine/serine-rich 4 (SRp75); similar to splicing factor, arginine/serine-rich 4 (SFRS4) (H. sapiens) (LOC139801), mRNA.
XM_067087	LOC140123		Homo sapiens similar to RNA binding protein (LOC140123), mRNA.
XM_067844	LOC132430		Homo sapiens similar to poly(A)-binding protein, cytoplasmic 4 (inducible form); inducible poly(A)-binding protein (LOC132430), mRNA.
XM_070624	LOC137819		Homo sapiens similar to Rbm (H. sapiens) (LOC137819), mRNA.
BC005054		AAH05054	Homo sapiens, clone IMAGE:2822202, mRNA, partial cds.
NM_031994	RNF17	NP_114383	Homo sapiens ring finger protein 17 (RNF17), transcript variant short, mRNA.

Nucleotide GenBank Accession Number or Manufacturer Sequence ID	Gene Name or Manufacturer Probe Name	Protein Product GeneBank Accsssion Number or Manufacturer Sequence Reference	Description
HSU87589		AAB63112	Human endogenous retrovirus clone K1.1 polymerase mRNA, partial cds.
XM_085111	LOC145359	XP_085111	Homo sapiens similar to Ribonuclease pancreatic precursor (RNase 1) (RNase A) (LOC145359), mRNA.
NM_024045	DDX50	NP_076950	Homo sapiens DEAD (Asp-Glu-Ala-Asp) box polypeptide 50 (DDX50), mRNA.
NM_001021	RPS17	NP_001012	Homo sapiens ribosomal protein S17 (RPS17), mRNA.
AC004957			Homo sapiens PAC clone RP5-1093O17 from 7, complete sequence.
NM_004792	PPIG	NP_004783	Homo sapiens peptidyl-prolyl isomerase G (cyclophilin G) (PPIG), mRNA.
NM_001011	RPS7	NP_001002	Homo sapiens ribosomal protein S7 (RPS7), mRNA.
XM_047920	LOC92906	XP_047920	Homo sapiens similar to Unknown (protein for IMAGE:3587716) (LOC92906), mRNA.
AI088192			oz97g12.x1 Soares_parathyroid_tumor_NbHPA Homo sapiens cDNA clone IMAGE:1683334 3' similar to TR:Q38800 Q388 COL-O PUTATIVE RNA HELICASE A. ;, mRNA sequence.
NM_005058	RBMY1A1	NP_005049	Homo sapiens RNA binding motif protein, Y-linked, family 1, member A1 (RBMY1A1), mRNA.
XM_060628	LOC127722	XP_060628	Homo sapiens similar to Heterogeneous nuclear ribonucleoprotein A1 (Helix-destabilizing protein) (Single-strand binding protein) (hnRNP core protein A1) (HDP-1) (Topoisomerase-inhibitor suppressed) (LOC127722), mRNA.
NM_020967	NCOA5	NP_066018	Homo sapiens nuclear receptor coactivator 5 (NCOA5), mRNA.
NM_006275	SFRS6	NP_006266	Homo sapiens splicing factor, arginine/serine-rich 6 (SFRS6), mRNA.
XM_088640	LOC158685	XP_088640	Homo sapiens similar to bA353C18.3.2 (splicing factor CC1.3, isoform 2 (CC1.4)) (LOC158685), mRNA.
XM_017931	LOC158201	XP_017931	Homo sapiens similar to Heterogeneous nuclear ribonucleoprotein G (hnRNP G) (Glycoprotein P43) (LOC158201), mRNA.
NM_005016	PCBP2	NP_005007	Homo sapiens poly(rC) binding protein 2 (PCBP2), transcript variant 1, mRNA.
NM_006713	PC4	NP_006704	Homo sapiens activated RNA polymerase II transcription cofactor 4 (PC4), mRNA.
NM_018427	RRN3	NP_060897	Homo sapiens RNA polymerase I transcription factor RRN3 (RRN3), mRNA.
NM_004960	FUS	NP_004951	Homo sapiens fusion (involved in t(12;16) in malignant liposarcoma) (FUS), mRNA.
AF267533		AAF78955	Homo sapiens CUG-binding protein LYLQ isoform mRNA, complete cds.
XM_062047	LOC120470	XP_062047	Homo sapiens similar to discs, large (Drosophila) homolog 2; chapsyn-110 (LOC120470), mRNA.

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Nucleotide GenBank Accession Number or Manufacturer Sequence ID	Gene Name or Manufacturer Probe Name	Protein Product GeneBank Accsssion Number or Manufacturer Sequence Reference	Description
NM_003797	EED	NP_003788	Homo sapiens embryonic ectoderm development (EED), transcript variant 1, mRNA.
NM_001025	RPS23	NP_001016	Homo sapiens ribosomal protein S23 (RPS23), mRNA.
NM_005156	ROD1	NP_005147	Homo sapiens ROD1 regulator of differentiation 1 (S. pombe) (ROD1), mRNA.
BC001050	NFATC3	AAH01050	Homo sapiens nuclear factor of activated T-cells, cytoplasmic, calcineurin-dependent 3, transcript variant 1, mRNA (cDNA clone MGC:1495 IMAGE:3505967), complete cds.
NM_000281	PCBD	NP_000272	Homo sapiens 6-pyruvoyl-tetrahydropterin synthase/dimerization cofactor of hepatocyte nuclear factor 1 alpha (TCF1) (PCBD), mRNA.
XM_068997	LOC134759	XP_068997	Homo sapiens similar to heterogeneous nuclear ribonucleoprotein L (LOC134759), mRNA.
NM_005887	DLEU1	NP_005878	Homo sapiens deleted in lymphocytic leukemia, 1 (DLEU1), mRNA.
AF435977	SON	AAL30810	Homo sapiens negative regulatory element-binding protein (SON) mRNA, complete cds, alternatively spliced.
NM_001002	RPLP0	NP_000993	Homo sapiens ribosomal protein, large, P0 (RPLP0), transcript variant 1, mRNA.
NM_000989	RPL30	NP_000980	Homo sapiens ribosomal protein L30 (RPL30), mRNA.
XM_087697	LOC153522	XP_087697	Homo sapiens similar to splicing factor, arginine/serine-rich 11 (LOC153522), mRNA.
AC004957			Homo sapiens PAC clone RP5-1093O17 from 7, complete sequence.
NM_004902	RNPC2	NP_004893	Homo sapiens RNA-binding region (RNP1, RRM) containing 2 (RNPC2), transcript variant 2, mRNA.
NM_003191	TARS	NP_003182	Homo sapiens threonyl-tRNA synthetase (TARS), mRNA.
NM_021177	LSM2	NP_067000	Homo sapiens LSM2 homolog, U6 small nuclear RNA associated (S. cerevisiae) (LSM2), mRNA.
NM_002948	RPL15	NP_002939	Homo sapiens ribosomal protein L15 (RPL15), mRNA.
XM_061850	LOC120083	XP_061850	Homo sapiens similar to 46kD arginine/serine-rich splicing factor [Homo sapiens] (LOC120083), mRNA.
NM_004705	PRKRIR	NP_004696	Homo sapiens protein-kinase, interferon-inducible double stranded RNA dependent inhibitor, repressor of (P58 repressor) (PRKRIR), mRNA.
XM_093219	LOC170270	XP_093219	Homo sapiens similar to Heterogeneous nuclear ribonucleoprotein A3 homolog 2 (hnRNP A3(B)) (LOC170270), mRNA.
HSPOP1	pop1	CAA67684	H.sapiens mRNA for Pop1 protein.
NM_001429	EP300	NP_001420	Homo sapiens E1A binding protein p300 (EP300), mRNA.

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Nucleotide GenBank Accession Number or Manufacturer Sequence ID	Gene Name or Manufacturer Probe Name	Protein Product GeneBank Accsssion Number or Manufacturer Sequence Reference	Description
NM_014168	HSPC133	NP_054887	Homo sapiens HSPC133 protein (HSPC133), mRNA.
NM_001968	EIF4E	NP_001959	Homo sapiens eukaryotic translation initiation factor 4E (EIF4E), mRNA.
NM_005968	HNRPM	NP_005959	Homo sapiens heterogeneous nuclear ribonucleoprotein M (HNRPM), transcript variant 1, mRNA.
NM_006372	SYNCRIP	NP_006363	Homo sapiens synaptotagmin binding, cytoplasmic RNA interacting protein (SYNCRIP), mRNA.
NM_002136	HNRPA1	NP_002127	Homo sapiens heterogeneous nuclear ribonucleoprotein A1 (HNRPA1), transcript variant 1, mRNA.
NM_006638	RPP40	NP_006629	Homo sapiens ribonuclease P 40kDa subunit (RPP40), mRNA.
NM_004539	NARS	NP_004530	Homo sapiens asparaginyl-tRNA synthetase (NARS), mRNA.
AC004957			Homo sapiens PAC clone RP5-1093O17 from 7, complete sequence.
HS164F3	dJ164F3.1	CAB55879	Human DNA sequence from clone RP1-164F3 on chromosome Xq21.33-23 Contains genes for DFN1 (deafness, X-linked 1 progressive, DDP (X-LINKED DEAFNESS DYSTONIA PROTEIN)), BTK(Bruton agammaglobulinemia tyrosine kinase), RPL44(L44-like ribosomal protein), GLA (galactosidase, alpha) and FTP3 (HETEROGENEOUS NUCLEAR RIBONUCLEOPROTEIN), ESTs, STSs, GSSs and CpG Islands, complete sequence.
BC016283	ABCE1	AAH16283	Homo sapiens ATP-binding cassette, sub-family E (OABP), member 1, mRNA (cDNA clone MGC:9023 IMAGE:3909151), complete cds.
NM_006392	NOL5A	NP_006383	Homo sapiens nucleolar protein 5A (56kDa with KKE/D repeat) (NOL5A), mRNA.
BC002395	SF3A3	AAH02395	Homo sapiens splicing factor 3a, subunit 3, 60kDa, mRNA (cDNA clone MGC:8445 IMAGE:2821350), complete cds.
NM_003769	SFRS9	NP_003760	Homo sapiens splicing factor, arginine/serine-rich 9 (SFRS9), mRNA.
NM_006743	RBM3	NP_006734	Homo sapiens RNA binding motif protein 3 (RBM3), mRNA.
AF165518	MAGOH	AAF86648	Homo sapiens MAGOH isoform (MAGOH) mRNA, complete cds.
NM_001402	EEF1A1	NP_001393	Homo sapiens eukaryotic translation elongation factor 1 alpha 1 (EEF1A1), mRNA.
NM_030594	CPEB1	NP_085097	Homo sapiens cytoplasmic polyadenylation element binding protein 1 (CPEB1), mRNA.
NM_001024	RPS21	NP_001015	Homo sapiens ribosomal protein S21 (RPS21), mRNA.

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Nucleotide GenBank Accession Number or Manufacturer Sequence ID	Gene Name or Manufacturer Probe Name	Protein Product GeneBank Accsssion Number or Manufacturer Sequence Reference	Description
NM_003488	AKAP1	NP_003479	Homo sapiens A kinase (PRKA) anchor protein 1 (AKAP1), nuclear gene encoding mitochondrial protein, transcript variant mRNA.
AF038362	TAF-172	AAC04573	Homo sapiens TBP-associated factor 172 (TAF-172) mRNA, complete cds.
NM_004501	HNRPU	NP_004492	Homo sapiens heterogeneous nuclear ribonucleoprotein U (scaffold attachment factor A) (HNRPU), transcript variant 2, mRNA.
NM_004396	DDX5	NP_004387	Homo sapiens DEAD (Asp-Glu-Ala-Asp) box polypeptide 5 (DDX5), mRNA.
NM_000968	RPL4	NP_000959	Homo sapiens ribosomal protein L4 (RPL4), mRNA.
NM_001028	RPS25	NP_001019	Homo sapiens ribosomal protein S25 (RPS25), mRNA.
NM_007367	RALY	NP_031393	Homo sapiens RNA binding protein (autoantigenic, hnRNP-associated with lethal yellow) (RALY), transcript variant 2, mRN,
NM_004689	MTA1	NP_004680	Homo sapiens metastasis associated 1 (MTA1), mRNA.
XM_068457	LOC133655	XP_068457	Homo sapiens similar to splicing coactivator subunit SRm300; RNA binding protein; AT-rich element binding factor; serine/arginine repetitive matrix 2 (LOC133655), mRNA.
NM_003754	EIF3S5	NP_003745	Homo sapiens eukaryotic translation initiation factor 3, subunit 5 epsilon, 47kDa (EIF3S5), mRNA.
AC004957			Homo sapiens PAC clone RP5-1093O17 from 7, complete sequence.
AC004957			Homo sapiens PAC clone RP5-1093O17 from 7, complete sequence.
NM_006711	RNPS1	NP_006702	Homo sapiens RNA binding protein S1, serine-rich domain (RNPS1), transcript variant 1, mRNA.
NM_016480	PAIP2	NP_057564	Homo sapiens poly(A) binding protein interacting protein 2 (PAIP2), mRNA.
NM_001014	RPS10	NP_001005	Homo sapiens ribosomal protein S10 (RPS10), mRNA.
AF070668		AAD20974	Homo sapiens 40S ribosomal protein S27 isoform mRNA, complete cds.
NM_006938	SNRPD1	NP_008869	Homo sapiens small nuclear ribonucleoprotein D1 polypeptide 16kDa (SNRPD1), mRNA.
NM_014892	RBM16	NP_055707	Homo sapiens RNA binding motif protein 16 (RBM16), mRNA.
NM_018353	C14orf106	NP_060823	Homo sapiens chromosome 14 open reading frame 106 (C14orf106), mRNA.
NM_006196	PCBP1	NP_006187	Homo sapiens poly(rC) binding protein 1 (PCBP1), mRNA.
XM_058819	MSI2	XP_058819	Homo sapiens musashi homolog 2 (Drosophila) (MSI2), mRNA.

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Nucleotide GenBank Accession Number or Manufacturer Sequence ID	Gene Name or Manufacturer Probe Name	Protein Product GeneBank Accsssion Number or Manufacturer Sequence Reference	Description
NM_003133	SRP9	NP_003124	Homo sapiens signal recognition particle 9kDa (SRP9), mRNA.
NM_001016	RPS12	NP_001007	Homo sapiens ribosomal protein S12 (RPS12), mRNA.
NM_004516	ILF3	NP_004507	Homo sapiens interleukin enhancer binding factor 3, 90kDa (ILF3), transcript variant 2, mRNA.
XM_058653	LOC122651	XP_058653	Homo sapiens LOC122651 (LOC122651), mRNA.
NM_003750	EIF3S10	NP_003741	Homo sapiens eukaryotic translation initiation factor 3, subunit 10 theta, 150/170kDa (EIF3S10), mRNA.
AK054960			Homo sapiens cDNA FLJ30398 fis, clone BRACE2008402, highly similar to Homo sapiens steroid receptor RNA activator isoform 3 mRNA.
NM_017697	FLJ20171	NP_060167	Homo sapiens hypothetical protein FLJ20171 (FLJ20171), mRNA.
NM_000985	RPL17	NP_000976	Homo sapiens ribosomal protein L17 (RPL17), mRNA.
HSM801037			Homo sapiens mRNA; cDNA DKFZp434L1935 (from clone DKFZp434L1935).
NM_014060	MCTS1	NP_054779	Homo sapiens malignant T cell amplified sequence 1 (MCTS1), mRNA.
NM_014463	LSM3	NP_055278	Homo sapiens LSM3 homolog, U6 small nuclear RNA associated (S. cerevisiae) (LSM3), mRNA.
AF294007		AAG31577	Homo sapiens haplotype 1 eosinophil-derived neurotoxin gene, complete cds.
NM_003092	SNRPB2	NP_003083	Homo sapiens small nuclear ribonucleoprotein polypeptide B" (SNRPB2), transcript variant 1, mRNA.
NM_001418	EIF4G2	NP_001409	Homo sapiens eukaryotic translation initiation factor 4 gamma, 2 (EIF4G2), mRNA.
NM_006802	SF3A3	NP_006793	Homo sapiens splicing factor 3a, subunit 3, 60kDa (SF3A3), mRNA.
XM_093626	LOC152108	XP_093626	Homo sapiens similar to ubiquitin A-52 residue ribosomal protein fusion product 1 (LOC152108), mRNA.
BC000138	HNRPM	AAH00138	Homo sapiens heterogeneous nuclear ribonucleoprotein M, transcript variant 1, mRNA (cDNA clone MGC:5136 IMAGE:2900532), complete cds.
NM_007040	HNRPUL1	NP_008971	Homo sapiens heterogeneous nuclear ribonucleoprotein U-like 1 (HNRPUL1), transcript variant 1, mRNA.
NM_003908	EIF2S2	NP_003899	Homo sapiens eukaryotic translation initiation factor 2, subunit 2 beta, 38kDa (EIF2S2), mRNA.
NM_000994	RPL32	NP_000985	Homo sapiens ribosomal protein L32 (RPL32), mRNA.
NM_003757	EIF3S2	NP_003748	Homo sapiens eukaryotic translation initiation factor 3, subunit 2 beta, 36kDa (EIF3S2), mRNA.
NM_080632	UPF3B	NP_542199	Homo sapiens UPF3 regulator of nonsense transcripts homolog B (yeast) (UPF3B), transcript variant 1, mRNA.

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Nucleotide GenBank Accession Number or Manufacturer Sequence ID	Gene Name or Manufacturer Probe Name	Protein Product GeneBank Accsssion Number or Manufacturer Sequence Reference	Description
AB002310	KIAA0312	BAA20771	Homo sapiens mRNA for KIAA0312 gene, partial cds.
NM_001005	RPS3	NP_000996	Homo sapiens ribosomal protein S3 (RPS3), mRNA.
NM_016638	ARL6IP4	NP_057722	Homo sapiens ADP-ribosylation-like factor 6 interacting protein 4 (ARL6IP4), mRNA.
NM_018387	STRBP	NP_060857	Homo sapiens spermatid perinuclear RNA binding protein (STRBP), mRNA.
NM_001212	C1QBP	NP_001203	Homo sapiens complement component 1, q subcomponent binding protein (C1QBP), nuclear gene encoding mitochondrial protein, mRNA.
NM_004985	KRAS2	NP_004976	Homo sapiens v-Ki-ras2 Kirsten rat sarcoma 2 viral oncogene homolog (KRAS2), transcript variant b, mRNA.
XM_061002	LOC118523	XP_061002	Homo sapiens LOC118523 (LOC118523), mRNA.
NM_003799	RNMT	NP_003790	Homo sapiens RNA (guanine-7-) methyltransferase (RNMT), mRNA.
NM_021190	PTBP2	NP_067013	Homo sapiens polypyrimidine tract binding protein 2 (PTBP2), mRNA.
NM_030980	FLJ12671	NP_112242	Homo sapiens hypothetical protein FLJ12671 (FLJ12671), mRNA.
NM_000971	RPL7	NP_000962	Homo sapiens ribosomal protein L7 (RPL7), mRNA.
NM_000995	RPL34	NP_000986	Homo sapiens ribosomal protein L34 (RPL34), transcript variant 1, mRNA.
NM_007006	CPSF5	NP_008937	Homo sapiens cleavage and polyadenylation specific factor 5, 25 kDa (CPSF5), mRNA.
NM_003429	ZNF85	NP_003420	Homo sapiens zinc finger protein 85 (HPF4, HTF1) (ZNF85), mRNA.
NM_006112	PPIE	NP_006103	Homo sapiens peptidylprolyl isomerase E (cyclophilin E) (PPIE), transcript variant 1, mRNA.
NM_014502	PRP19	NP_055317	Homo sapiens PRP19/PSO4 homolog (S. cerevisiae) (PRP19), mRNA.
AC004858	WUGSC:H_DJ0687K01.2	AAF19255	Homo sapiens PAC clone RP4-687K1 from 14, complete sequence.
XM_060358	LOC127164	XP_060358	Homo sapiens similar to TAR DNA binding protein (LOC127164), mRNA.
NM_003819	PABPC4	NP_003810	Homo sapiens poly(A) binding protein, cytoplasmic 4 (inducible form) (PABPC4), mRNA.
AB014564	KIAA0664	BAA31639	Homo sapiens mRNA for KIAA0664 protein, partial cds.
NM_022170	WBSCR1	NP_071496	Homo sapiens Williams-Beuren syndrome chromosome region 1 (WBSCR1), transcript variant 1, mRNA.
NM_005087	FXR1	NP_005078	Homo sapiens fragile X mental retardation, autosomal homolog 1 (FXR1), mRNA.
NM_003680	YARS	NP_003671	Homo sapiens tyrosyl-tRNA synthetase (YARS), mRNA.

Nucleotide GenBank Accession Number or Manufacturer Sequence ID	Gene Name or Manufacturer Probe Name	Protein Product GeneBank Accsssion Number or Manufacturer Sequence Reference	Description
NM_004500	HNRPC	NP_004491	Homo sapiens heterogeneous nuclear ribonucleoprotein C (C1/C2) (HNRPC), transcript variant 2, mRNA.
AC004858	WUGSC:H_DJ0687K01.2	AAF19255	Homo sapiens PAC clone RP4-687K1 from 14, complete sequence.
NM_002887	RARS	NP_002878	Homo sapiens arginyl-tRNA synthetase (RARS), mRNA.
NM_020414	DDX24	NP_065147	Homo sapiens DEAD (Asp-Glu-Ala-Asp) box polypeptide 24 (DDX24), mRNA.
NM_014871	USP52	NP_055686	Homo sapiens ubiquitin specific protease 52 (USP52), mRNA.
XM_063601	LOC123341	XP_063601	Homo sapiens similar to Heterogeneous nuclear ribonucleoprotein A1 (Helix-destabilizing protein) (Single-strand binding protein) (hnRNP core protein A1) (HDP) (LOC123341), mRNA.
NM_000988	RPL27	NP_000979	Homo sapiens ribosomal protein L27 (RPL27), mRNA.
AF266720S4	RBMX	AAK58567	Homo sapiens RBMX (RBMX) gene, exons 6 through 9 and complete cds.
NM_001967	EIF4A2	NP_001958	Homo sapiens eukaryotic translation initiation factor 4A, isoform 2 (EIF4A2), mRNA.
XM_059612	LOC132928	XP_059612	Homo sapiens similar to polyA binding protein (AA 1-633) (LOC132928), mRNA.
NM_018959	DAZAP1	NP_061832	Homo sapiens DAZ associated protein 1 (DAZAP1), transcript variant 2, mRNA.
NM_004294	MTRF1	NP_004285	Homo sapiens mitochondrial translational release factor 1 (MTRF1), nuclear gene encoding mitochondrial protein, mRNA.
NM_001031	RPS28	NP_001022	Homo sapiens ribosomal protein S28 (RPS28), mRNA.
AB046830	KIAA1610	BAB13436	Homo sapiens mRNA for KIAA1610 protein, partial cds.
NM_007358	M96	NP_031384	Homo sapiens likely ortholog of mouse metal response element binding transcription factor 2 (M96), mRNA.
AF083441		AAD52028	Homo sapiens SUI1 isolog mRNA, complete cds.
NM_014393	STAU2	NP_055208	Homo sapiens staufen, RNA binding protein, homolog 2 (Drosophila) (STAU2), mRNA.
NM_017544	NRF	NP_060014	Homo sapiens NF-kappa B-repressing factor (NRF), mRNA.
AF155096		AAD42862	Homo sapiens NY-REN-6 antigen mRNA, partial cds.
NM_015703	CGI-96	NP_056518	Homo sapiens CGI-96 protein (CGI-96), mRNA.
NM_021993	FUSIP2	NP_068833	Homo sapiens FUS interacting protein (serine-arginine rich) 2 (FUSIP2), mRNA.
NM_001970	EIF5A	NP_001961	Homo sapiens eukaryotic translation initiation factor 5A (EIF5A), mRNA.

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Nucleotide GenBank Accession Number or Manufacturer Sequence ID	Gene Name or Manufacturer Probe Name	Protein Product GeneBank Accsssion Number or Manufacturer Sequence Reference	Description
NM_012322	LSM5	NP_036454	Homo sapiens LSM5 homolog, U6 small nuclear RNA associated (S. cerevisiae) (LSM5), mRNA.
NM_003142	SSB	NP_003133	Homo sapiens Sjogren syndrome antigen B (autoantigen La) (SSB), mRNA.
NM_003017	SFRS3	NP_003008	Homo sapiens splicing factor, arginine/serine-rich 3 (SFRS3), mRNA.
AC004957			Homo sapiens PAC clone RP5-1093O17 from 7, complete sequence.
NM_001019	RPS15A	NP_001010	Homo sapiens ribosomal protein S15a (RPS15A), mRNA.
NM_005782	THOC4	NP_005773	Homo sapiens THO complex 4 (THOC4), mRNA.
NM_006924	SFRS1	NP_008855	Homo sapiens splicing factor, arginine/serine-rich 1 (splicing factor 2, alternate splicing factor) (SFRS1), mRNA.
NM_031369	HNRPD	NP_112737	Homo sapiens heterogeneous nuclear ribonucleoprotein D (AU-rich element RNA binding protein 1, 37kDa) (HNRPD), transcript variant 2, mRNA.
NM_020690	MASK	NP_065741	Homo sapiens multiple ankyrin repeats, single KH-domain (MASK) homolog (MASK), mRNA.
NM_016047	P14	NP_057131	Homo sapiens pre-mRNA branch site protein p14 (P14), mRNA.
NM_004953	EIF4G1	NP_004944	Homo sapiens eukaryotic translation initiation factor 4 gamma, 1 (EIF4G1), transcript variant 5, mRNA.
NM_006625	FUSIP1	NP_006616	Homo sapiens FUS interacting protein (serine-arginine rich) 1 (FUSIP1), transcript variant 1, mRNA.
NM_021104	RPL41	NP_066927	Homo sapiens ribosomal protein L41 (RPL41), mRNA.
NM_001751	CARS	NP_001742	Homo sapiens cysteinyl-tRNA synthetase (CARS), transcript variant 2, mRNA.
NM_001533	HNRPL	NP_001524	Homo sapiens heterogeneous nuclear ribonucleoprotein L (HNRPL), mRNA.
NM_004397	DDX6	NP_004388	Homo sapiens DEAD (Asp-Glu-Ala-Asp) box polypeptide 6 (DDX6), mRNA.
NM_005762	TRIM28	NP_005753	Homo sapiens tripartite motif-containing 28 (TRIM28), mRNA.
NM_003756	EIF3S3	NP_003747	Homo sapiens eukaryotic translation initiation factor 3, subunit 3 gamma, 40kDa (EIF3S3), mRNA.
NM_022551	RPS18	NP_072045	Homo sapiens ribosomal protein S18 (RPS18), mRNA.
NM_020365	EIF2B3	NP_065098	Homo sapiens eukaryotic translation initiation factor 2B, subunit 3 gamma, 58kDa (EIF2B3), mRNA.
XM_047499	LOC149603	XP_047499	Homo sapiens hypothetical protein LOC149603 (LOC149603), mRNA.
NM_006548	IMP-2	NP_006539	Homo sapiens IGF-II mRNA-binding protein 2 (IMP-2), mRNA.
NM_000984	RPL23A	NP_000975	Homo sapiens ribosomal protein L23a (RPL23A), mRNA.

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Nucleotide GenBank Accession Number or Manufacturer Sequence ID	Gene Name or Manufacturer Probe Name	Protein Product GeneBank Accsssion Number or Manufacturer Sequence Reference	Description
NM_001022	RPS19	NP_001013	Homo sapiens ribosomal protein S19 (RPS19), mRNA.
NM_005617	RPS14	NP_005608	Homo sapiens ribosomal protein S14 (RPS14), mRNA.
NM_003187	TAF9	NP_003178	Homo sapiens TAF9 RNA polymerase II, TATA box binding protein (TBP)-associated factor, 32kDa (TAF9), transcript varian 1, mRNA.
NM_006386	DDX17	NP_006377	Homo sapiens DEAD (Asp-Glu-Ala-Asp) box polypeptide 17 (DDX17), transcript variant 1, mRNA.
NM_000990	RPL27A	NP_000981	Homo sapiens ribosomal protein L27a (RPL27A), mRNA.
NM_005850	SF3B4	NP_005841	Homo sapiens splicing factor 3b, subunit 4, 49kDa (SF3B4), mRNA.
AC004957			Homo sapiens PAC clone RP5-1093O17 from 7, complete sequence.
NM_003729	RTCD1	NP_003720	Homo sapiens RNA terminal phosphate cyclase domain 1 (RTCD1), mRNA.
NM_006451	PAIP1	NP_006442	Homo sapiens poly(A) binding protein interacting protein 1 (PAIP1), transcript variant 1, mRNA.
NM_002137	HNRPA2B1	NP_002128	Homo sapiens heterogeneous nuclear ribonucleoprotein A2/B1 (HNRPA2B1), transcript variant A2, mRNA.
NM_001009	RPS5	NP_001000	Homo sapiens ribosomal protein S5 (RPS5), mRNA.
NM_005646	TARBP1	NP_005637	Homo sapiens TAR (HIV) RNA binding protein 1 (TARBP1), mRNA.
NM_015646	RAP1B	NP_056461	Homo sapiens RAP1B, member of RAS oncogene family (RAP1B), mRNA.
XM_064113	LOC124380	XP_064113	Homo sapiens LOC124380 (LOC124380), mRNA.
NM_004697	PRPF4	NP_004688	Homo sapiens PRP4 pre-mRNA processing factor 4 homolog (yeast) (PRPF4), mRNA.
AC004957			Homo sapiens PAC clone RP5-1093O17 from 7, complete sequence.
NM_001358	DHX15	NP_001349	Homo sapiens DEAH (Asp-Glu-Ala-His) box polypeptide 15 (DHX15), mRNA.
NM_005520	HNRPH1	NP_005511	Homo sapiens heterogeneous nuclear ribonucleoprotein H1 (H) (HNRPH1), mRNA.
NM_003333	UBA52	NP_003324	Homo sapiens ubiquitin A-52 residue ribosomal protein fusion product 1 (UBA52), mRNA.
XM_098297	LOC153028	XP_098297	Homo sapiens similar to RNA binding protein S1, serine-rich domain (H. sapiens) (LOC153028), mRNA.
NM_006559	KHDRBS1	NP_006550	Homo sapiens KH domain containing, RNA binding, signal transduction associated 1 (KHDRBS1), mRNA.
BC000595	DDX17	AAH00595	Homo sapiens DEAD (Asp-Glu-Ala-Asp) box polypeptide 17, mRNA (cDNA clone MGC:2030 IMAGE:3345982), complete cds.
NM_001006	RPS3A	NP_000997	Homo sapiens ribosomal protein S3A (RPS3A), mRNA.

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Nucleotide GenBank Accession Number or Manufacturer Sequence ID	Gene Name or Manufacturer Probe Name	Protein Product GeneBank Accsssion Number or Manufacturer Sequence Reference	Description
NM_005870	SAP18	NP_005861	Homo sapiens sin3-associated polypeptide, 18kDa (SAP18), mRNA.
NM_014412	SIP	NP_055227	Homo sapiens Siah-interacting protein (SIP), mRNA.
NM_007104	RPL10A	NP_009035	Homo sapiens ribosomal protein L10a (RPL10A), mRNA.
NM_005121	THRAP1	NP_005112	Homo sapiens thyroid hormone receptor associated protein 1 (THRAP1), mRNA.
NM_080663	MGC16943	NP_542394	Homo sapiens similar to RIKEN cDNA 4933424N09 gene (MGC16943), mRNA.
NM_006074	TRIM22	NP_006065	Homo sapiens tripartite motif-containing 22 (TRIM22), mRNA.
NM_002950	RPN1	NP_002941	Homo sapiens ribophorin I (RPN1), mRNA.
XM_062934	LOC122056	XP_062934	Homo sapiens similar to ATP-dependent RNA helicase A (Nuclear DNA helicase II) (NDH II) (DEAD-box protein 9) (LOC122056), mRNA.
NM_033117	RBM18	NP_149108	Homo sapiens RNA binding motif protein 18 (RBM18), mRNA.
NM_005034	POLR2K	NP_005025	Homo sapiens polymerase (RNA) II (DNA directed) polypeptide K, 7.0kDa (POLR2K), mRNA.
NM_006805	HNRPA0	NP_006796	Homo sapiens heterogeneous nuclear ribonucleoprotein A0 (HNRPA0), mRNA.
NM_002696	POLR2G	NP_002687	Homo sapiens polymerase (RNA) II (DNA directed) polypeptide G (POLR2G), mRNA.
NM_002140	HNRPK	NP_002131	Homo sapiens heterogeneous nuclear ribonucleoprotein K (HNRPK), transcript variant 1, mRNA.
XM_053153	LOC149973	XP_053153	Homo sapiens similar to RNA binding motif protein, X chromosome (H. sapiens) (LOC149973), mRNA.
XM_070603	LOC137784	XP_070603	Homo sapiens similar to ANTIGEN GOR (LOC137784), mRNA.
NM_002938	RNF4	NP_002929	Homo sapiens ring finger protein 4 (RNF4), mRNA.
XM_086419	LOC149092	XP_086419	Homo sapiens similar to pumilio homolog 1 (Drosophila) (H. sapiens) (LOC149092), mRNA.
AC004957			Homo sapiens PAC clone RP5-1093O17 from 7, complete sequence.
NM_002520	NPM1	NP_002511	Homo sapiens nucleophosmin (nucleolar phosphoprotein B23, numatrin) (NPM1), mRNA.
NM_005437	NCOA4	NP_005428	Homo sapiens nuclear receptor coactivator 4 (NCOA4), mRNA.
NM_001000	RPL39	NP_000991	Homo sapiens ribosomal protein L39 (RPL39), mRNA.
NM_000969	RPL5	NP_000960	Homo sapiens ribosomal protein L5 (RPL5), mRNA.
NM_000973	RPL8	NP_000964	Homo sapiens ribosomal protein L8 (RPL8), transcript variant 1, mRNA.
NM_003651	CSDA	NP_003642	Homo sapiens cold shock domain protein A (CSDA), mRNA.

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Nucleotide GenBank Accession Number or Manufacturer Sequence ID	Gene Name or Manufacturer Probe Name	Protein Product GeneBank Accession Number or Manufacturer Sequence Reference	Description
XM_067918	LOC132583	XP_067918	Homo sapiens similar to HETEROGENEOUS NUCLEAR RIBONUCLEOPROTEIN A1 (HELIX-DESTABILIZING PROTEIN) (SINGLE-STRAND BINDING PROTEIN) (HNRNP CORE PROTEIN A1) (LOC132583), mRNA.
NM_006450	SPF45	NP_006441	Homo sapiens splicing factor (45kD) (SPF45), mRNA.
NM_014912	CPEB3	NP_055727	Homo sapiens cytoplasmic polyadenylation element binding protein 3 (CPEB3), mRNA.
NM_001326	CSTF3	NP_001317	Homo sapiens cleavage stimulation factor, 3' pre-RNA, subunit 3, 77kDa (CSTF3), mRNA.
NM_004940	DDX7	NP_004931	Homo sapiens DEAD/H (Asp-Glu-Ala-Asp/His) box polypeptide 7 (RNA helicase, 52kDa) (DDX7), mRNA.
NM_005021	ENPP3	NP_005012	Homo sapiens ectonucleotide pyrophosphatase/phosphodiesterase 3 (ENPP3), mRNA.
NM_006047	RBM12	NP_006038	Homo sapiens RNA binding motif protein 12 (RBM12), transcript variant 1, mRNA.
NM_014676	PUM1	NP_055491	Homo sapiens pumilio homolog 1 (Drosophila) (PUM1), mRNA.
NM_002786	PSMA1	NP_002777	Homo sapiens proteasome (prosome, macropain) subunit, alpha type, 1 (PSMA1), transcript variant 2, mRNA.
HUMNUCTIAR		AAA36384	Homo sapiens nucleolysin TIAR mRNA, complete cds.
XM_086011	LOC148027	XP_086011	Homo sapiens similar to bruno-like 5, RNA binding protein (Drosophila); Bruno (Drosophila) -like 5, RNA binding protein; CUG-BP and ETR-3 like factor 5; RNA-binding protein BRUNOL-5 (LOC148027), mRNA.
NM_000967	RPL3	NP_000958	Homo sapiens ribosomal protein L3 (RPL3), mRNA.
NM_014071	NCOA6	NP_054790	Homo sapiens nuclear receptor coactivator 6 (NCOA6), mRNA.
XM_073386	LOC119594	XP_073386	Homo sapiens similar to SPLICING FACTOR U2AF 65 KDA SUBUNIT (U2 AUXILIARY FACTOR 65 KDA SUBUNIT) (U2 SNRNP AUXILIARY FACTOR LARGE SUBUNIT) (U2AF65) (LOC119594), mRNA.
NM_000982	RPL21	NP_000973	Homo sapiens ribosomal protein L21 (RPL21), mRNA.
AF062105	IGH	AAC18141	Homo sapiens clone 21u-19 immunoglobulin heavy chain variable region (IGH) mRNA, partial cds.
NM_006414	RPP38	NP_006405	Homo sapiens ribonuclease P/MRP 38kDa subunit (RPP38), transcript variant 2, mRNA.
NM_004599	SREBF2	NP_004590	Homo sapiens sterol regulatory element binding transcription factor 2 (SREBF2), mRNA.
NM_007273	REA	NP_009204	Homo sapiens repressor of estrogen receptor activity (REA), mRNA.
NM_002453	MTIF2	NP_002444	Homo sapiens mitochondrial translational initiation factor 2 (MTIF2), nuclear gene encoding mitochondrial protein, mRNA.

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Nucleotide GenBank Accession Number or Manufacturer Sequence ID	Gene Name or Manufacturer Probe Name	Protein Product GeneBank Accsssion Number or Manufacturer Sequence Reference	Description
AF380184	SON	AAL34502	Homo sapiens SON DNA binding protein isoform F (SON) mRNA, complete cds, alternatively spliced.
HUMRNAHELA	DDX9	AAB48855	Human RNA helicase A mRNA, complete cds.
NM_006929	SKIV2L	NP_008860	Homo sapiens superkiller viralicidic activity 2-like (S. cerevisiae) (SKIV2L), mRNA.
AK001652		BAA91812	Homo sapiens cDNA FLJ10790 fis, clone NT2RP4000518, weakly similar to ATP-DEPENDENT RNA HELICASE ROK1.
AF037448	GRY-RBP	AAC12926	Homo sapiens RRM RNA binding protein Gry-rbp (GRY-RBP) mRNA, complete cds.
NM_000977	RPL13	NP_000968	Homo sapiens ribosomal protein L13 (RPL13), transcript variant 1, mRNA.
NM_016024	CGI-79	NP_057108	Homo sapiens CGI-79 protein (CGI-79), mRNA.
AB044971	nopp34	BAB41210	Homo sapiens mRNA for nucleolar phosphoprotein Nopp34, complete cds.
NM_000996	RPL35A	NP_000987	Homo sapiens ribosomal protein L35a (RPL35A), mRNA.
NM_031277	RNF17	NP_112567	Homo sapiens ring finger protein 17 (RNF17), transcript variant long, mRNA.
XM_067051	LOC140065	XP_067051	Homo sapiens similar to RNA binding motif protein, Y chromosome, family 1 member A1 (RNA-binding motif protein 1) (LOC140065), mRNA.
NM_006276	SFRS7	NP_006267	Homo sapiens splicing factor, arginine/serine-rich 7, 35kDa (SFRS7), mRNA.
NM_005008	NHP2L1	NP_004999	Homo sapiens NHP2 non-histone chromosome protein 2-like 1 (S. cerevisiae) (NHP2L1), mRNA.
NM_003138	SRPK2	NP_003129	Homo sapiens SFRS protein kinase 2 (SRPK2), mRNA.
XM_092386	LOC165115	XP_092386	Homo sapiens similar to KIAA1841 protein (LOC165115), mRNA.
XM_062047	LOC120470	XP_062047	Homo sapiens similar to discs, large (Drosophila) homolog 2; chapsyn-110 (LOC120470), mRNA.
NM_000991	RPL28	NP_000982	Homo sapiens ribosomal protein L28 (RPL28), mRNA.
NM_001537	HSBP1	NP_001528	Homo sapiens heat shock factor binding protein 1 (HSBP1), mRNA.
AB025254		BAA76379	Homo sapiens mRNA for tudor repeat associator with PCTAIRE 2, partial cds.
NM_006696	BRD8	NP_006687	Homo sapiens bromodomain containing 8 (BRD8), transcript variant 1, mRNA.
NM_030941	LOC81691	NP_112203	Homo sapiens exonuclease NEF-sp (LOC81691), mRNA.
NM_016132	MYEF2	NP_057216	Homo sapiens myelin expression factor 2 (MYEF2), mRNA.
NM_004640	BAT1	NP_004631	Homo sapiens HLA-B associated transcript 1 (BAT1), transcript variant 1, mRNA.

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Nucleotide GenBank Accession Number or Manufacturer Sequence ID	Gene Name or Manufacturer Probe Name	Protein Product GeneBank Accession Number or Manufacturer Sequence Reference	Description
NM_012345	NUFIP1	NP_036477	Homo sapiens nuclear fragile X mental retardation protein interacting protein 1 (NUFIP1), mRNA.
XM_092031	LOC163147	XP_092031	Homo sapiens similar to Splicing factor 3A subunit 2 (Spliceosome associated protein 62) (SAP 62) (SF3a66) (LOC163147), mRNA.
XM_067074	LOC140100	XP_067074	Homo sapiens similar to RBM1 (LOC140100), mRNA.
NM_002047	GARS	NP_002038	Homo sapiens glycyl-tRNA synthetase (GARS), mRNA.
NM_001017	RPS13	NP_001008	Homo sapiens ribosomal protein S13 (RPS13), mRNA.
NM_004506	HSF2	NP_004497	Homo sapiens heat shock transcription factor 2 (HSF2), mRNA.
NM_012426	SF3B3	NP_036558	Homo sapiens splicing factor 3b, subunit 3, 130kDa (SF3B3), mRNA.
NM_019038	TDRD4	NP_061911	Homo sapiens tudor domain containing 4 (TDRD4), mRNA.
AC022517		AAF31271	Homo sapiens chromosome 19, BC335474 (CIT-HSPC_482H14), complete sequence.
NM_001111	ADAR	NP_001102	Homo sapiens adenosine deaminase, RNA-specific (ADAR), transcript variant ADAR-a, mRNA.
XM_060102	LOC126635	XP_060102	Homo sapiens LOC126635 (LOC126635), mRNA.
NM_017803	FLJ20399	NP_060273	Homo sapiens hypothetical protein FLJ20399 (FLJ20399), mRNA.
XM_001524	LOC151173	XP_001524	Homo sapiens similar to TAR DNA-binding protein-43 (TDP-43) (LOC151173), mRNA.
NM_004757	SCYE1	NP_004748	Homo sapiens small inducible cytokine subfamily E, member 1 (endothelial monocyte-activating) (SCYE1), mRNA.
NM_014003	DHX38	NP_054722	Homo sapiens DEAH (Asp-Glu-Ala-His) box polypeptide 38 (DHX38), mRNA.
XM_086792	LOC150152	XP_086792	Homo sapiens similar to SPLICING FACTOR U2AF 35 KD SUBUNIT (U2 AUXILIARY FACTOR 35 KD SUBUNIT) (U1 SNRNP AUXILIARY FACTOR SMALL SUBUNIT) (LOC150152), mRNA.
AC004957			Homo sapiens PAC clone RP5-1093O17 from 7, complete sequence.
NM_007007	CPSF6	NP_008938	Homo sapiens cleavage and polyadenylation specific factor 6, 68kDa (CPSF6), mRNA.
NM_019037	EXOSC4	NP_061910	Homo sapiens exosome component 4 (EXOSC4), mRNA.
XM_070605	LOC137786	XP_070605	Homo sapiens similar to ANTIGEN GOR (LOC137786), mRNA.
NM_017736	FLJ20274	NP_060206	Homo sapiens hypothetical protein FLJ20274 (FLJ20274), mRNA.
NM_018046	HSU84971	NP_060516	Homo sapiens vasculogenesis gene on 5q (HSU84971), mRNA.

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Nucleotide GenBank Accession Number or Manufacturer Sequence ID	Gene Name or Manufacturer Probe Name	Protein Product GeneBank Accsssion Number or Manufacturer Sequence Reference	Description
NM_006842	SF3B2	NP_006833	Homo sapiens splicing factor 3b, subunit 2, 145kD (SF3B2), mRNA.
NM_021033	RAP2A	NP_066361	Homo sapiens RAP2A, member of RAS oncogene family (RAP2A), mRNA.
XM_095899	LOC169732	XP_095899	Homo sapiens similar to EXOSOME COMPLEX EXONUCLEASE RRP4 (RIBOSOMAL RNA PROCESSING PROTEIN 4) (LOC169732), mRNA.
NM_031274	TEX13A	NP_112564	Homo sapiens testis expressed sequence 13A (TEX13A), mRNA.
NM_006387	CHERP	NP_006378	Homo sapiens calcium homeostasis endoplasmic reticulum protein (CHERP), mRNA.
NM_000964	RARA	NP_000955	Homo sapiens retinoic acid receptor, alpha (RARA), mRNA.
XM_066446	LOC139051	XP_066446	Homo sapiens similar to pol protein (LOC139051), mRNA.
NM_003072	SMARCA4	NP_003063	Homo sapiens SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 4 (SMARCA4), mRNA.
NM_022767	FLJ12484	NP_073604	Homo sapiens hypothetical protein FLJ12484 (FLJ12484), mRNA.
NM_001112	ADARB1	NP_001103	Homo sapiens adenosine deaminase, RNA-specific, B1 (RED1 homolog rat) (ADARB1), transcript variant DRADA2a, mRN.
NM_017774	CDKAL1	NP_060244	Homo sapiens CDK5 regulatory subunit associated protein 1-like 1 (CDKAL1), mRNA.
NM_013302	EEF2K	NP_037434	Homo sapiens elongation factor-2 kinase (EEF2K), mRNA.
NM_018702	ADARB2	NP_061172	Homo sapiens adenosine deaminase, RNA-specific, B2 (RED2 homolog rat) (ADARB2), mRNA.
XM_089765	LOC143344	XP_089765	Homo sapiens similar to poly(A) binding protein (LOC143344), mRNA.
AF026564	RBMII	AAC16916	Homo sapiens RNA binding protein II (RBMII) gene, complete cds.
NM_016333	SRRM2	NP_057417	Homo sapiens serine/arginine repetitive matrix 2 (SRRM2), mRNA.
NM_004039	ANXA2	NP_004030	Homo sapiens annexin A2 (ANXA2), mRNA.
NM_006187	OAS3	NP_006178	Homo sapiens 2'-5'-oligoadenylate synthetase 3, 100kDa (OAS3), mRNA.
XM_089587	LOC159428	XP_089587	Homo sapiens similar to EUKARYOTIC TRANSLATION INITIATION FACTOR 4B (EIF-4B) (LOC159428), mRNA.
AB061839	RPS9	BAB79477	Homo sapiens RPS9 gene for ribosomal protein S9, complete cds and sequence.
NM_018060	FLJ10326	NP_060530	Homo sapiens mitochondrial isoleucine tRNA synthetase (FLJ10326), mRNA.

Figure 14

Nucleotide GenBank Accession Number or Manufacturer Sequence ID	Gene Name or Manufacturer Probe Name	Protein Product GeneBank Accsssion Number or Manufacturer Sequence Reference	Description
NM_003787	NOL4	NP_003778	Homo sapiens nucleolar protein 4 (NOL4), mRNA.
NM_003086	SNAPC4	NP_003077	Homo sapiens small nuclear RNA activating complex, polypeptide 4, 190kDa (SNAPC4), mRNA.
NM_004728	DDX21	NP_004719	Homo sapiens DEAD (Asp-Glu-Ala-Asp) box polypeptide 21 (DDX21), mRNA.
XM_092043	LOC163160	XP_092043	Homo sapiens similar to polypyrimidine tract binding protein, isoform b; heterogeneous nuclear ribonucleoprotein polypeptic I; RNA binding protein (LOC163160), mRNA.
NM_014829	DDX46	NP_055644	Homo sapiens DEAD (Asp-Glu-Ala-Asp) box polypeptide 46 (DDX46), mRNA.
NM_004597	SNRPD2	NP_004588	Homo sapiens small nuclear ribonucleoprotein D2 polypeptide 16.5kDa (SNRPD2), transcript variant 1, mRNA.
NM_004774	PPARBP	NP_004765	Homo sapiens PPAR binding protein (PPARBP), mRNA.
NM_002515	NOVA1	NP_002506	Homo sapiens neuro-oncological ventral antigen 1 (NOVA1), transcript variant 1, mRNA.
NM_006410	HTATIP2	NP_006401	Homo sapiens HIV-1 Tat interactive protein 2, 30kDa (HTATIP2), mRNA.
NM_005687	FARSLB	NP_005678	Homo sapiens phenylalanine-tRNA synthetase-like, beta subunit (FARSLB), mRNA.
NM_001644	APOBEC1	NP_001635	Homo sapiens apolipoprotein B mRNA editing enzyme, catalytic polypeptide 1 (APOBEC1), transcript variant 1, mRNA.
NM_033246	PML	NP_150249	Homo sapiens promyelocytic leukemia (PML), transcript variant 7, mRNA.
XM_091270	LOC161983	XP_091270	Homo sapiens similar to Heterogeneous nuclear ribonucleoprotein A1 (Helix-destabilizing protein) (Single-strand binding protein) (hnRNP core protein A1) (HDP-1) (Topoisomerase-inhibitor suppressed) (LOC161983), mRNA.
NM_015409	EP400	NP_056224	Homo sapiens E1A binding protein p400 (EP400), mRNA.
NM_015453	DKFZP434F091	NP_056268	Homo sapiens DKFZP434F091 protein (DKFZP434F091), mRNA.
XM_067072	LOC140098	XP_067072	Homo sapiens similar to RBM1 (LOC140098), mRNA.
XM_056568	LOC147774	XP_056568	Homo sapiens similar to KH-type splicing regulatory protein (FUSE binding protein 2) (H. sapiens) (LOC147774), mRNA.
NM_022078	FLJ12455	NP_071361	Homo sapiens hypothetical protein FLJ12455 (FLJ12455), mRNA.
NM_001364	DLG2	NP_001355	Homo sapiens discs, large homolog 2, chapsyn-110 (Drosophila) (DLG2), mRNA.

Figure 14

Nucleotide GenBank Accession Number or Manufacturer Sequence ID	Gene Name or Manufacturer Probe Name	Protein Product GeneBank Accsssion Number or Manufacturer Sequence Reference	Description
NM_003752	EIF3S8	NP_003743	Homo sapiens eukaryotic translation initiation factor 3, subunit 8, 110kDa (EIF3S8), mRNA.
XM_091235	LOC161931	XP_091235	Homo sapiens similar to testis nuclear RNA binding protein; testis nuclear RNA-binding protein (LOC161931), mRNA.
NM_014977	ACINUS	NP_055792	Homo sapiens apoptotic chromatin condensation inducer in the nucleus (ACINUS), mRNA.
NM_000461	THRB	NP_000452	Homo sapiens thyroid hormone receptor, beta (erythroblastic leukemia viral (v-erb-a) oncogene homolog 2, avian) (THRB), mRNA.
NM_024939	FLJ21918	NP_079215	Homo sapiens hypothetical protein FLJ21918 (FLJ21918), mRNA.
NM_032572	RNASE7	NP_115961	Homo sapiens ribonuclease, RNase A family, 7 (RNASE7), mRNA.
AF315592	PUMH1	AAG31807	Homo sapiens Pumilio 1 (PUMH1) mRNA, complete cds.
NM_004433	ELF3	NP_004424	Homo sapiens E74-like factor 3 (ets domain transcription factor, epithelial-specific) (ELF3), mRNA.
XM_058943	LOC125925	XP_058943	Homo sapiens similar to R32611_1 (LOC125925), mRNA.
NM_006624	BS69	NP_006615	Homo sapiens adenovirus 5 E1A binding protein (BS69), mRNA.
NM_016166	PIAS1	NP_057250	Homo sapiens protein inhibitor of activated STAT, 1 (PIAS1), mRNA.
NM_006663	RAI	NP_006654	Homo sapiens RelA-associated inhibitor (RAI), mRNA.
XM_058876	MGC49942	XP_058876	Homo sapiens hypothetical protein MGC49942 (MGC49942), mRNA.
NM_000057	BLM	NP_000048	Homo sapiens Bloom syndrome (BLM), mRNA.
NM_004461	FARSLA	NP_004452	Homo sapiens phenylalanine-tRNA synthetase-like, alpha subunit (FARSLA), mRNA.
NM_006163	NFE2	NP_006154	Homo sapiens nuclear factor (erythroid-derived 2), 45kDa (NFE2), mRNA.
AE006640	NDUFB10	AAK61302	Homo sapiens 16p13.3 sequence section 8 of 8.
NM_017846	SECP43	NP_060316	Homo sapiens tRNA selenocysteine associated protein (SECP43), mRNA.
XM_088975	LOC148683	XP_088975	Homo sapiens similar to pumilio homolog 1 (Drosophila); pumilio (Drosophila) homolog 1 (LOC148683), mRNA.
NM_012321	LSM4	NP_036453	Homo sapiens LSM4 homolog, U6 small nuclear RNA associated (S. cerevisiae) (LSM4), mRNA.
NM_012143	TFIP11	NP_036275	Homo sapiens tuftelin interacting protein 11 (TFIP11), mRNA.
NM_001111	ADAR	NP_001102	Homo sapiens adenosine deaminase, RNA-specific (ADAR), transcript variant ADAR-a, mRNA.

Figure 14

Nucleotide GenBank Accession Number or Manufacturer Sequence ID	Gene Name or Manufacturer Probe Name	Protein Product GeneBank Accession Number or Manufacturer Sequence Reference	Description
NM_001535	HRMT1L1	NP_001526	Homo sapiens HMT1 hnRNP methyltransferase-like 1 (S. cerevislae) (HRMT1L1), mRNA.
NM_016173	HEMK	NP_057257	Homo sapiens HEMK homolog 7kb (HEMK), mRNA.
NM_005754	G3BP	NP_005745	Homo sapiens Ras-GTPase-activating protein SH3-domain-binding protein (G3BP), transcript variant 1, mRNA
NM_002892	ARID4A	NP_002883	Homo sapiens AT rich interactive domain 4A (RBP1-like) (ARID4A), transcript variant 1, mRNA.
XM_092221	LOC164891	XP_092221	Homo sapiens similar to mRNA for ribosomal protein S9 (LOC164891), mRNA.
NM_001412	EIF1A	NP_001403	Homo sapiens eukaryotic translation initiation factor 1A (EIF1A), mRNA.
XM_095591	LOC169242	XP_095591	Homo sapiens similar to data source:SPTR, source key:O94865, evidence:ISS~homolog to KIAA0765 PROTEIN (HRIHFB2091 PROTEIN) (FRAGMENT)~putative (LOC169242), mRNA.
NM_033004	NALP1	NP_127497	Homo sapiens NACHT, leucine rich repeat and PYD containing 1 (NALP1), transcript variant 1, mRNA.
XM_093336	LOC165631	XP_093336	Homo sapiens similar to Eukaryotic translation initiation factor 4B (eIF-4B) (LOC165631), mRNA.
NM_012255	XRN2	NP_036387	Homo sapiens 5'-3' exoribonuclease 2 (XRN2), mRNA.
XM_065002	LOC126246	XP_065002	Homo sapiens LOC126246 (LOC126246), mRNA.
NM_001618	ADPRT	NP_001609	Homo sapiens ADP-ribosyltransferase (NAD+; poly (ADP-ribose) polymerase) (ADPRT), mRNA.
XM_067452	LOC131596	XP_067452	Homo sapiens similar to splicing factor 3a, subunit 2, 66kD; Spliceosome protein SAP-62 (LOC131596), mRNA.
XM_062601	LOC121365	XP_062601	Homo sapiens similar to RBM1 (LOC121365), mRNA.
HUMAUA		AAB59352	Homo sapiens (clone JH4B1) PM-scl autoantigen mRNA, complete cds.
NM_001686	ATP5B	NP_001677	Homo sapiens ATP synthase, H+ transporting, mitochondrial F1 complex, beta polypeptide (ATP5B), mRNA.
NM_007294	BRCA1	NP_009225	Homo sapiens breast cancer 1, early onset (BRCA1), transcript variant BRCA1a, mRNA.
NM_002502	NFKB2	NP_002493	Homo sapiens nuclear factor of kappa light polypeptide gene enhancer in B-cells 2 (p49/p100) (NFKB2), mRNA.
XM_068248	LOC133225	XP_068248	Homo sapiens similar to heterogeneous ribonuclear particle protein A1.beta - human (LOC133225), mRNA.
NM_021724	NR1D1	NP_068370	Homo sapiens nuclear receptor subfamily 1, group D, member 1 (NR1D1), mRNA.
NM_016374	ARID4B	NP_057458	Homo sapiens AT rich interactive domain 4B (RBP1- like) (ARID4B), transcript variant 1, mRNA.

Figure 14

Nucleotide GenBank Accession Number or Manufacturer Sequence ID	Gene Name or Manufacturer Probe Name	Protein Product GeneBank Accsssion Number or Manufacturer Sequence Reference	Description
XM_068022	LOC132772	XP_068022	Homo sapiens similar to split ends; polycephalon; yippee interacting protein 1 (LOC132772), mRNA.
NM_005548	KARS	NP_005539	Homo sapiens lysyl-tRNA synthetase (KARS), mRNA.
NM_006311	NCOR1	NP_006302	Homo sapiens nuclear receptor co-repressor 1 (NCOR1), mRNA.
NM_016505	PS1D	NP_057589	Homo sapiens putative S1 RNA binding domain protein (PS1D), mRNA.
NM_004719	SFRS2IP	NP_004710	Homo sapiens splicing factor, arginine/serine-rich 2, interacting protein (SFRS2IP), mRNA.
NM_003686	EXO1	NP_003677	Homo sapiens exonuclease 1 (EXO1), transcript variant 3, mRNA.
NM_005481	THRAP5	NP_005472	Homo sapiens thyroid hormone receptor associated protein 5 (THRAP5), mRNA.
NM_002296	LBR	NP_002287	Homo sapiens lamin B receptor (LBR), transcript variant 1, mRNA.
NM_014966	DHX30	NP_055781	Homo sapiens DEAH (Asp-Glu-Ala-His) box polypeptide 30 (DHX30), transcript variant 2, mRNA.
AF026126	HNRPD	AAC23476	Homo sapiens heterogeneous nuclear ribonucleoprotein D (HNRPD) gene, complete cds.
XM_066901	LOC139801	XP_066901	Homo sapiens LOC139801 (LOC139801), mRNA.
AK057303		BAB71416	Homo sapiens cDNA FLJ32741 fis, clone TESTI2001345, highly similar to M.musculus Tenr mRNA for RNA binding protein
XM_067087	LOC140123	XP_067087	Homo sapiens similar to RNA binding motif protein, Y chromosome, family 2 member B (LOC140123), mRNA.
NM_033502	TRERF1	NP_277037	Homo sapiens transcriptional regulating factor 1 (TRERF1), transcript variant 1, mRNA.
NM_005822	DSCR1L1	NP_005813	Homo sapiens Down syndrome critical region gene 1-like 1 (DSCR1L1), mRNA.
NM_002897	RBMS1	NP_002888	Homo sapiens RNA binding motif, single stranded interacting protein 1 (RBMS1), transcript variant scr2, mRNA.
XM_067844	LOC132430	XP_067844	Homo sapiens similar to Polyadenylate-binding protein 4 (Poly(A)-binding protein 4) (PABP 4) (Inducible poly(A)-binding protein) (iPABP) (Activated-platelet protein-1) (APP-1) (LOC132430), mRNA.
NM_002949	MRPL12	NP_002940	Homo sapiens mitochondrial ribosomal protein L12 (MRPL12), nuclear gene encoding mitochondrial protein, mRNA.
NM_003219	TERT	NP_003210	Homo sapiens telomerase reverse transcriptase (TERT), transcript variant 1, mRNA.
XM_070624	LOC137819	XP_070624	Homo sapiens LOC137819 (LOC137819), mRNA.

Figure 14

Nucleotide GenBank Accession Number or Manufacturer Sequence ID	Gene Name or Manufacturer Probe Name	Protein Product GeneBank Accsssion Number or Manufacturer Sequence Reference	Description
NM_002937	RNASE4	NP_002928	Homo sapiens ribonuclease, RNase A family, 4 (RNASE4), transcript variant 2, mRNA.
NM_006546	IMP-1	NP_006537	Homo sapiens IGF-II mRNA-binding protein 1 (IMP-1), mRNA.
NM_004860	FXR2	NP_004851	Homo sapiens fragile X mental retardation, autosomal homolog 2 (FXR2), mRNA.
NM_003321	TUFM	NP_003312	Homo sapiens Tu translation elongation factor, mitochondrial (TUFM), mRNA.
NM_005693	NR1H3	NP_005684	Homo sapiens nuclear receptor subfamily 1, group H, member 3 (NR1H3), mRNA.
NM_006565	CTCF	NP_006556	Homo sapiens CCCTC-binding factor (zinc finger protein) (CTCF), mRNA.
NM_018664	SNFT	NP_061134	Homo sapiens Jun dimerization protein p21SNFT (SNFT), mRNA.
M_000938	POLR2B	NP_000929	Homo sapiens polymerase (RNA) II (DNA directed) polypeptide B, 140kDa (POLR2B), mRNA.
M_002934	RNASE2	NP_002925	Homo sapiens ribonuclease, RNase A family, 2 (liver, eosinophil-derived neurotoxin) (RNASE2), mRNA.
M_006980	MTERF	NP_008911	Homo sapiens transcription termination factor, mitochondrial (MTERF), nuclear gene encoding mitochondrial protein, mRNA

Figure 14

GenBank Accession for mRNA	Gene Symbol	GenBank Accession for Protein	Nucleotide Sequence Description
NM_012070	ATRN	NP_036202	Homo sapiens attractin (ATRN), transcript variant 3, mRNA.
NM_003488	AKAP1	NP_003479	Homo sapiens A kinase (PRKA) anchor protein 1 (AKAP1), nuclear gene encoding mitochondrial protein, transcript variant 1, mRNA.
XM_044795	LOC92392	XP_044795	Homo sapiens similar to colon cancer antigen NY-CO-45 (LOC92392), mRNA.
XM_089332	LOC149382	XP_089332	Homo sapiens similar to ribosomal protein L22 proprotein; 60S ribosomal protein L22; Epstein-Barr-encoded RNA-associated protein; Epstein-Barr virus small RNA-associated protein; EBER-associated protein; heparin-binding protein 15; heparin-binding protein HBp15... (LOC149382), mRNA.
NM_001024	RPS21	NP_001015	Homo sapiens ribosomal protein S21 (RPS21), mRNA.
NM_001324	CSTF1	NP_001315	Homo sapiens cleavage stimulation factor, 3' pre-RNA, subunit 1, 50kDa (CSTF1), mRNA.
NM_006625	FUSIP1	NP_006616	Homo sapiens FUS interacting protein (serine-arginine rich) 1 (FUSIP1), transcript variant 1, mRNA.
NM_006540	NCOA2	NP_006531	Homo sapiens nuclear receptor coactivator 2 (NCOA2), mRNA.
NM_005782	THOC4	NP_005773	Homo sapiens THO complex 4 (THOC4), mRNA.
NM_032102	SRP46	NP_115285	Homo sapiens Splicing factor, arginine/serine-rich, 46kD (SRP46), mRNA.
NM_014497	NP220	NP_055312	Homo sapiens NP220 nuclear protein (NP220), mRNA.
_022915	MRPL44	NP_075066	Homo sapiens mitochondrial ribosomal protein L44 (MRPL44), nuclear gene encoding mitochondrial protein, mRNA.
_003325	HIRA	NP_003316	Homo sapiens HIR histone cell cycle regulation defective homolog A (S. cerevisiae) (HIRA), mRNA.
_006397	RNASEH2A	NP_006388	Homo sapiens ribonuclease H2, large subunit (RNASEH2A), mRNA.
_006548	IMP-2	NP_006539	Homo sapiens IGF-II mRNA-binding protein 2 (IMP-2), mRNA.
_005801	SUI1	NP_005792	Homo sapiens putative translation initiation factor (SUI1), mRNA.
007157		AAC19158	Homo sapiens clone 23856 unknown mRNA, partial cds.
_000029	AGT	NP_000020	Homo sapiens angiotensinogen (serine (or cysteine) proteinase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 8) (AGT), mRNA.
_002904	RDBP	NP_002895	Homo sapiens RD RNA binding protein (RDBP), mRNA.
BC016283	ABCE1	AAH16283	Homo sapiens ATP-binding cassette, sub-family E (OABP), member 1, mRNA (cDNA clone MGC:9023 IMAGE:3909151), complete cds.
AF049525	HYPC	AAC27503	Homo sapiens huntingtin-interacting protein HYPC (HYPC) mRNA, partial cds.
NM_014462	LSM1	NP_055277	Homo sapiens LSM1 homolog, U6 small nuclear RNA associated (S. cerevisiae) (LSM1), mRNA.

Figure 15

GenBank Accession for mRNA	Gene Symbol	GenBank Accession for Protein	Nucleotide Sequence Description
AB014564	KIAA0664	BAA31639	Homo sapiens mRNA for KIAA0664 protein, partial cds.
NM_001253	CDC5L	NP_001244	Homo sapiens CDC5 cell division cycle 5-like (S. pombe) (CDC5L), mRNA.
NM_001991	EZH1	NP_001982	Homo sapiens enhancer of zeste homolog 1 (Drosophila) (EZH1), mRNA.
NM_001090	ABCF1	NP_001081	Homo sapiens ATP-binding cassette, sub-family F (GCN20), member 1 (ABCF1), mRNA.
NM_000061	BTK	NP_000052	Homo sapiens Bruton agammaglobulinemia tyrosine kinase (BTK), mRNA.
AB020657	KIAA0850	BAA74873	Homo sapiens mRNA for KIAA0850 protein, partial cds.
NM_032390	MKI67IP	NP_115766	Homo sapiens MKI67 (FHA domain) interacting nucleolar phosphoprotein (MKI67IP), mRNA.
NM_030980	FLJ12671	NP_112242	Homo sapiens hypothetical protein FLJ12671 (FLJ12671), mRNA.
I_017827	SARS2	NP_060297	Homo sapiens seryl-tRNA synthetase 2 (SARS2), mRNA.
I_066948	LOC139891	XP_066948	Homo sapiens similar to hypothetical protein BC011593 (LOC139891), mRNA.
I_091974	LOC147891	XP_091974	Homo sapiens similar to hypothetical protein DKFZp434I1930 (H. sapiens) (LOC147891), mRNA.
I_014060	MCTS1	NP_054779	Homo sapiens malignant T cell amplified sequence 1 (MCTS1), mRNA.
I_000647	CCR2	NP_000638	Homo sapiens chemokine (C-C motif) receptor 2 (CCR2), transcript variant A, mRNA.
I_001016	RPS12	NP_001007	Homo sapiens ribosomal protein S12 (RPS12), mRNA.
NM_032359	MGC4308	NP_115735	Homo sapiens hypothetical protein MGC4308 (MGC4308), mRNA.
NM_017736	FLJ20274	NP_060206	Homo sapiens hypothetical protein FLJ20274 (FLJ20274), mRNA.
NM_006627	POP4	NP_006618	Homo sapiens processing of precursor 4, ribonuclease P/MRP subunit (S. cerevisiae) (POP4), mRNA.
BC001050	NFATC3	AAH01050	Homo sapiens nuclear factor of activated T-cells, cytoplasmic, calcineurin-dependent 3, transcript variant 1, mRNA (cDNA clone MGC:1495 IMAGE:3505967), complete cds.
NM_000344	SMN1	NP_000335	Homo sapiens survival of motor neuron 1, telomeric (SMN1), transcript variant d, mRNA.

Figure 16 (1)

GenBank Accession for mRNA	Gene Symbol	GenBank Accession for Protein	Nucleotide Sequence Description
XM_094140	LOC166863	XP_094140	Homo sapiens similar to Apobec-1 complementation factor, APOBEC-1 stimulating protein (LOC166863), mRNA.
NM_005548	KARS	NP_005539	Homo sapiens lysyl-tRNA synthetase (KARS), mRNA.
NM_007235	XPOT	NP_009166	Homo sapiens exportin, tRNA (nuclear export receptor for tRNAs) (XPOT), mRNA.
AF230402		AAG50181	Homo sapiens tripartite motif protein TRIM19 beta mRNA, complete cds.
NM_003680	YARS	NP_003671	Homo sapiens tyrosyl-tRNA synthetase (YARS), mRNA.
XM_086419	LOC149092	XP_086419	Homo sapiens similar to pumilio homolog 1 (Drosophila) (H. sapiens) (LOC149092), mRNA.
NM_015629	PRPF31	NP_056444	Homo sapiens PRP31 pre-mRNA processing factor 31 homolog (yeast) (PRPF31), mRNA.
XM_067598	LOC131898	XP_067598	Homo sapiens similar to POLYADENYLATE-BINDING PROTEIN 2 (POLY(A) BINDING PROTEIN 2) (PABP 2) (LOC131898), mRNA.
?1255	EIF2C2	AAF13034	Homo sapiens protein translation initiation factor 2C2 (EIF2C2) mRNA, partial cds.
)8670 8	LOC149816	XP_086708	Homo sapiens similar to Splicing factor 3A subunit 3 (Spliceosome associated protein 61) (SAP 61) (SF3a60) (LOC149816), mRNA.
00702 0	U1SNRNPBP	NP_008951	Homo sapiens U1-snRNP binding protein homolog (U1SNRNPBP), transcript variant 1, mRNA.
01745 3	STAU	NP_059347	Homo sapiens staufen, RNA binding protein (Drosophila) (STAU), transcript variant T3, mRNA.
00169 8	AUH	NP_001689	Homo sapiens AU RNA binding protein/enoyl-Coenzyme A hydratase (AUH), nuclear gene encoding mitochondrial protein, mRNA.
00171 4	BICD1	NP_001705	Homo sapiens Bicaudal D homolog 1 (Drosophila) (BICD1), mRNA.
XM_066904	LOC139804	XP_066904	Homo sapiens similar to testes-specific heterogenous nuclear ribonucleoprotein G-T (LOC139804), mRNA.
NM_004593	SFRS10	NP_004584	Homo sapiens splicing factor, arginine/serine-rich 10 (transformer 2 homolog, Drosophila) (SFRS10), mRNA.
AL117507	DKFZp434F1935	CAB55969	Homo sapiens mRNA; cDNA DKFZp434F1935 (from clone DKFZp434F1935); partial cds.

Figure 16 (2)

GenBank Accession for mRNA	Gene Symbol	GenBank Accession for Protein	Nucleotide Sequence Description
AB020657	KIAA0850	BAA74873	Homo sapiens mRNA for KIAA0850 protein, partial cds.
AB033019	KIAA1193	BAA86507	Homo sapiens mRNA for KIAA1193 protein, partial cds.
AF026564	RBMII	AAC16916	Homo sapiens RNA binding protein II (RBMII) gene, complete cds.
AF165518	MAGOH	AAF86648	Homo sapiens MAGOH isoform (MAGOH) mRNA, complete cds.
AF273304		AAF98162	Homo sapiens XPMC2 protein mRNA, complete cds.
AL117507	DKFZp434F1935	CAB55969	Homo sapiens mRNA; cDNA DKFZp434F1935 (from clone DKFZp434F1935); partial cds.
L01457		AAB59352	Homo sapiens (clone JH4B1) PM-scl autoantigen mRNA, complete cds.
NM_000455	STK11	NP_000446	Homo sapiens serine/threonine kinase 11 (Peutz-Jeghers syndrome) (STK11), mRNA.
NM_000982	RPL21	NP_000973	Homo sapiens ribosomal protein L21 (RPL21), mRNA.
NM_000996	RPL35A	NP_000987	Homo sapiens ribosomal protein L35a (RPL35A), mRNA.
NM_000999	RPL38	NP_000990	Homo sapiens ribosomal protein L38 (RPL38), mRNA.
NM_001004	RPLP2	NP_000995	Homo sapiens ribosomal protein, large P2 (RPLP2), mRNA.
NM_001011	RPS7	NP_001002	Homo sapiens ribosomal protein S7 (RPS7), mRNA.
_001026	RPS24	NP_001017	Homo sapiens ribosomal protein S24 (RPS24), transcript variant 2, mRNA.
_001032	RPS29	NP_001023	Homo sapiens ribosomal protein S29 (RPS29), mRNA.
_001112	ADARB1	NP_001103	Homo sapiens adenosine deaminase, RNA-specific, B1 (RED1 homolog rat) (ADARB1), transcript variant DRADA2a, mRNA.
_001356	DDX3X	NP_001347	Homo sapiens DEAD (Asp-Glu-Ala-Asp) box polypeptide 3, X-linked (DDX3X), transcript variant 2, mRNA.
_001357	DHX9	NP_001348	Homo sapiens DEAH (Asp-Glu-Ala-His) box polypeptide 9 (DHX9), transcript variant 1, mRNA.
_001618	ADPRT	NP_001609	Homo sapiens ADP-ribosyltransferase (NAD+; poly (ADP-ribose) polymerase) (ADPRT), mRNA.
_002520	NPM1	NP_002511	Homo sapiens nucleophosmin (nucleolar phosphoprotein B23, numatrin) (NPM1), mRNA.
_002967	SAFB	NP_002958	Homo sapiens scaffold attachment factor B (SAFB), mRNA.
_003133	SRP9	NP_003124	Homo sapiens signal recognition particle 9kDa (SRP9), mRNA.
NM_003429	ZNF85	NP_003420	Homo sapiens zinc finger protein 85 (HPF4, HTF1) (ZNF85), mRNA.
NM_003472	DEK	NP_003463	Homo sapiens DEK oncogene (DNA binding) (DEK), mRNA.
NM_003675	PRPF18	NP_003666	Homo sapiens PRP18 pre-mRNA processing factor 18 homolog (yeast) (PRPF18), mRNA.
NM_003895	SYNJ1	NP_003886	Homo sapiens synaptojanin 1 (SYNJ1), transcript variant 1, mRNA.
NM_004169	SHMT1	NP_004160	Homo sapiens serine hydroxymethyltransferase 1 (soluble) (SHMT1), transcript variant 1, mRNA.
NM_004289	NFE2L3	NP_004280	Homo sapiens nuclear factor (erythroid-derived 2)-like 3 (NFE2L3), mRNA.
NM_004396	DDX5	NP_004387	Homo sapiens DEAD (Asp-Glu-Ala-Asp) box polypeptide 5 (DDX5), mRNA.
NM_004990	MARS	NP_004981	Homo sapiens methionine-tRNA synthetase (MARS), mRNA.
NM_005083	U2AF1L1	NP_005074	Homo sapiens U2(RNU2) small nuclear RNA auxiliary factor 1-like 1 (U2AF1L1), mRNA.
NM_005548	KARS	NP_005539	Homo sapiens lysyl-tRNA synthetase (KARS), mRNA.
NM_006624	BS69	NP_006615	Homo sapiens adenovirus 5 E1A binding protein (BS69), mRNA.

Figure 17(11

GenBank Accession for mRNA	Gene Symbol	GenBank Accession for Protein	Nucleotide Sequence Description
NM_007020	U1SNRNPBP	NP_008951	Homo sapiens U1-snRNP binding protein homolog (U1SNRNPBP), transcript variant 1, mRNA.
NM_007080	LSM6	NP_009011	Homo sapiens LSM6 homolog, U6 small nuclear RNA associated (S. cerevisiae) (LSM6), mRNA.
NM_007362	NCBP2	NP_031388	Homo sapiens nuclear cap binding protein subunit 2, 20kDa (NCBP2), mRNA.
NM_012255	XRN2	NP_036387	Homo sapiens 5'-3' exoribonuclease 2 (XRN2), mRNA.
NM_012423	RPL13A	NP_036555	Homo sapiens ribosomal protein L13a (RPL13A), mRNA.
NM_014977	ACINUS	NP_055792	Homo sapiens apoptotic chromatin condensation inducer in the nucleus (ACINUS), mRNA.
NM_015934	NOP5/NOP58	NP_057018	Homo sapiens nucleolar protein NOP5/NOP58 (NOP5/NOP58), mRNA.
NM_016480	PAIP2	NP_057564	Homo sapiens poly(A) binding protein interacting protein 2 (PAIP2), mRNA.
NM_017840	MRPL16	NP_060310	Homo sapiens mitochondrial ribosomal protein L16 (MRPL16), nuclear gene encoding mitochondrial protein, mRNA.
NM_018281	FLJ10948	NP_060751	Homo sapiens hypothetical protein FLJ10948 (FLJ10948), mRNA.
NM_018427	RRN3	NP_060897	Homo sapiens RNA polymerase I transcription factor RRN3 (RRN3), mRNA.
NM_018664	SNFT	NP_061134	Homo sapiens Jun dimerization protein p21SNFT (SNFT), mRNA.
NM_021104	RPL41	NP_066927	Homo sapiens ribosomal protein L41 (RPL41), mRNA.
_022551	RPS18	NP_072045	Homo sapiens ribosomal protein S18 (RPS18), mRNA.
_031210	DC50	NP_112487	Homo sapiens hypothetical protein DC50 (DC50), mRNA.
_001524	LOC151173	XP_001524	Homo sapiens similar to TAR DNA-binding protein-43 (TDP-43) (LOC151173), mRNA.
_016729	LOC157679	XP_016729	Homo sapiens similar to nuclear receptor coactivator 6 interacting protein (H. sapiens) (LOC157679), mRNA.
_031058	LOC147647	XP_031058	Homo sapiens similar to nucleolar protein interacting with the FHA domain of pKi-67 (H. sapiens) (LOC147647), mRNA.
_047920	LOC92906	XP_047920	Homo sapiens similar to Unknown (protein for IMAGE:3587716) (LOC92906), mRNA.
_058430	LOC119880	XP_058430	Homo sapiens similar to hypothetical protein similar to RNA-binding protein lark (LOC119880), mRNA.
_058943	LOC125925	XP_058943	Homo sapiens similar to R32611_1 (LOC125925), mRNA.
XM_059194	LOC127933	XP_059194	Homo sapiens hypothetical protein BC014917 (LOC127933), mRNA.
XM_059936	LOC138046	XP_059936	Homo sapiens similar to RNA-binding protein Raly (LOC138046), mRNA.
XM_060808	LOC128072	XP_060808	Homo sapiens similar to Vigilin (High density lipoprotein-binding protein) (HDL-binding protein) (LOC128072), mRNA.
XM_067452	LOC131596	XP_067452	Homo sapiens similar to splicing factor 3a, subunit 2, 66kD; Spliceosome protein SAP-62 (LOC131596), mRNA.
XM_068248	LOC133225	XP_068248	Homo sapiens similar to heterogeneous ribonuclear particle protein A1.beta - human (LOC133225), mRNA.
XM_068457	LOC133655	XP_068457	Homo sapiens similar to splicing coactivator subunit SRm300; RNA binding protein; AT-rich element binding factor; serine/arginine repetitive matrix 2 (LOC133655), mRNA.
XM_088640	LOC158685	XP_088640	Homo sapiens similar to bA353C18.3.2 (splicing factor CC1.3, isoform 2 (CC1.4)) (LOC158685),

Figure 17 (2)

GenBank Accession for mRNA	Gene Symbol	GenBank Accession for Protein	Nucleotide Sequence Description
			mRNA.
XM_093336	LOC165631	XP_093336	Homo sapiens similar to Eukaryotic translation initiation factor 4B (eIF-4B) (LOC165631), mRNA.
NM_000971	RPL7	NP_000962	Homo sapiens ribosomal protein L7 (RPL7), mRNA.

Figure 1)(3)

GenBank Accession for mRNA	Gene Symbol	GenBank Accession for Protein	Nucleotide Sequence Description
XM_091042	LOC161682	XP_091042	Homo sapiens similar to data source:MGD, source key:MGI:107795, evidence:ISS~heterogeneous nuclear ribonucleoprotein C~putative (LOC161682), mRNA.
XM_068433	LOC133616	XP_068433	Homo sapiens similar to Putative RNA-binding protein 15 (RNA binding motif protein 15) (One-twenty two protein) (LOC133616), mRNA.
XM_093259	LOC170330	XP_093259	Homo sapiens similar to RBM1 (LOC170330), mRNA.
XM_085059	LOC145223	XP_085059	Homo sapiens similar to Splicing factor 3B subunit 4 (Spliceosome associated protein 49) (SAP 49) (SF3b50) (Pre-mRNA splicing factor SF3b 49 kDa subunit) (LOC145223), mRNA.
AF121255	EIF2C2	AAF13034	Homo sapiens protein translation initiation factor 2C2 (EIF2C2) mRNA, partial cds.
NM_005664	MKRN3	NP_005655	Homo sapiens makorin, ring finger protein, 3 (MKRN3), mRNA.
NM_001357	DHX9	NP_001348	Homo sapiens DEAH (Asp-Glu-Ala-His) box polypeptide 9 (DHX9), transcript variant 1, mRNA.
NM_030941	LOC81691	NP_112203	Homo sapiens exonuclease NEF-sp (LOC81691), mRNA.
NM_014852	KIAA0682	NP_055667	Homo sapiens KIAA0682 gene product (KIAA0682), mRNA.
NM_000246	MHC2TA	NP_000237	Homo sapiens MHC class II transactivator (MHC2TA), mRNA.
NM_007165	SF3A2	NP_009096	Homo sapiens splicing factor 3a, subunit 2, 66kDa (SF3A2), mRNA.
NM_005384	NFIL3	NP_005375	Homo sapiens nuclear factor, interleukin 3 regulated (NFIL3), mRNA.
NM_018427	RRN3	NP_060897	Homo sapiens RNA polymerase I transcription factor RRN3 (RRN3), mRNA.
XM_060212	LOC126861	XP_060212	Homo sapiens similar to tudor repeat associator with PCTAIRE 2 (LOC126861), mRNA.
NM_004895	CIAS1	NP_004886	Homo sapiens cold autoinflammatory syndrome 1 (CIAS1), transcript variant 1, mRNA.
NM_003750	EIF3S10	NP_003741	Homo sapiens eukaryotic translation initiation factor 3, subunit 10 theta, 150/170kDa (EIF3S10), mRNA.
XM_092386	LOC165115	XP_092386	Homo sapiens similar to KIAA1841 protein (LOC165115), mRNA.
NM_007294	BRCA1	NP_009225	Homo sapiens breast cancer 1, early onset (BRCA1), transcript variant BRCA1a, mRNA.
NM_001991	EZH1	NP_001982	Homo sapiens enhancer of zeste homolog 1 (Drosophila) (EZH1), mRNA.
XM_010852	LOC151249	XP_010852	Homo sapiens similar to helix-destabilizing protein - rat (LOC151249), mRNA.
NM_002502	NFKB2	NP_002493	Homo sapiens nuclear factor of kappa light polypeptide gene enhancer in B-cells 2 (p49/p100) (NFKB2), mRNA.
NM_000946	PRIM1	NP_000937	Homo sapiens primase, polypeptide 1, 49kDa (PRIM1), mRNA.
NM_006893	LGTN	NP_008824	Homo sapiens ligatin (LGTN), mRNA.
XM_094140	LOC166863	XP_094140	Homo sapiens similar to Apobec-1 complementation factor, APOBEC-1 stimulating protein (LOC166863), mRNA.
AF083441		AAD52028	Homo sapiens SUI1 isolog mRNA, complete cds.
XM_068457	LOC133655	XP_068457	Homo sapiens similar to splicing coactivator subunit SRm300; RNA binding protein; AT-rich element binding factor; serine/arginine repetitive matrix 2 (LOC133655), mRNA.

Figure 18 (1)

GenBank Accession for mRNA	Gene Symbol	GenBank Accession for Protein	Nucleotide Sequence Description
NM_000125	ESR1	NP_000116	Homo sapiens estrogen receptor 1 (ESR1), mRNA.
NM_015971	MRPS7	NP_057055	Homo sapiens mitochondrial ribosomal protein S7 (MRPS7), nuclear gene encoding mitochondrial protein, mRNA.
NM_032514	MAP1LC3A	NP_115903	Homo sapiens microtubule-associated protein 1 light chain 3 alpha (MAP1LC3A), transcript variant 1, mRNA.
NM_004504	HRB	NP_004495	Homo sapiens HIV-1 Rev binding protein (HRB), mRNA.
NM_001029	RPS26	NP_001020	Homo sapiens ribosomal protein S26 (RPS26), mRNA.
NM_002535	OAS2	NP_002526	Homo sapiens 2'-5'-oligoadenylate synthetase 2, 69/71kDa (OAS2), transcript variant 2, mRNA.
NM_003325	HIRA	NP_003316	Homo sapiens HIR histone cell cycle regulation defective homolog A (S. cerevisiae) (HIRA), mRNA.

Figure 18(2)

GenBank Accession for mRNA	Gene Symbol	GenBank Accession for Protein	Nucleotide Sequence Description
XM_092652	LOC165534	XP_092652	Homo sapiens LOC165534 (LOC165534), mRNA.
NM_004705	PRKRIR	NP_004696	Homo sapiens protein-kinase, interferon-inducible double stranded RNA dependent inhibitor, repressor of (P58 repressor) (PRKRIR), mRNA.
NM_001537	HSBP1	NP_001528	Homo sapiens heat shock factor binding protein 1 (HSBP1), mRNA.
XM_070624	LOC137819	XP_070624	Homo sapiens LOC137819 (LOC137819), mRNA.
NM_006397	RNASEH2A	NP_006388	Homo sapiens ribonuclease H2, large subunit (RNASEH2A), mRNA.
NM_012423	RPL13A	NP_036555	Homo sapiens ribosomal protein L13a (RPL13A), mRNA.
XM_085059	LOC145223	XP_085059	Homo sapiens similar to Splicing factor 3B subunit 4 (Spliceosome associated protein 49) (SAP 49) (SF3b50) (Pre-mRNA splicing factor SF3b 49 kDa subunit) (LOC145223), mRNA.
NM_003136	SRP54	NP_003127	Homo sapiens signal recognition particle 54kDa (SRP54), mRNA.
XM_091653	LOC162582	XP_091653	Homo sapiens similar to HETEROGENEOUS NUCLEAR RIBONUCLEOPROTEIN A1 (HELIX-DESTABILIZING PROTEIN) (SINGLE-STRAND BINDING PROTEIN) (HNRNP CORE PROTEIN A1) (LOC162582), mRNA.
NM_005657	TP53BP1	NP_005648	Homo sapiens tumor protein p53 binding protein, 1 (TP53BP1), mRNA.
M_004491	GRLF1	NP_004482	Homo sapiens glucocorticoid receptor DNA binding factor 1 (GRLF1), transcript variant 2, mRNA.
M_007205	TREX2	NP_009136	Homo sapiens three prime repair exonuclease 2 (TREX2), transcript variant 1, mRNA.
M_006565	CTCF	NP_006556	Homo sapiens CCCTC-binding factor (zinc finger protein) (CTCF), mRNA.
AF026563	RBMII		Homo sapiens RBMII gene, exon 6.
M_007297	BRCA1	NP_009228	Homo sapiens breast cancer 1, early onset (BRCA1), transcript variant BRCA1-delta2-10, mRNA.
M_004559	NSEP1	NP_004550	Homo sapiens nuclease sensitive element binding protein 1 (NSEP1), mRNA.
M_060358	LOC127164	XP_060358	Homo sapiens similar to TAR DNA binding protein (LOC127164), mRNA.
M_003685	KHSRP	NP_003676	Homo sapiens KH-type splicing regulatory protein (FUSE binding protein 2) (KHSRP), mRNA.
M_005115	MVP	NP_005106	Homo sapiens major vault protein (MVP), transcript variant 2, mRNA.
M_002904	RDBP	NP_002895	Homo sapiens RD RNA binding protein (RDBP), mRNA.
M_005772	RCL1	NP_005763	Homo sapiens RNA terminal phosphate cyclase-like 1 (RCL1), mRNA.
X98494	mpp10	CAA67120	H.sapiens mRNA for M phase phosphoprotein 10.
NM_015062	PPRC1	NP_055877	Homo sapiens peroxisome proliferative activated receptor, gamma, coactivator-related 1 (PPRC1), mRNA.
AF083441		AAD52028	Homo sapiens SUI1 isolog mRNA, complete cds.
XM_068457	LOC133655	XP_068457	Homo sapiens similar to splicing coactivator subunit SRm300; RNA binding protein; AT-rich element binding factor; serine/arginine repetitive matrix 2 (LOC133655), mRNA.
AK000256		BAA91036	Homo sapiens cDNA FLJ20249 fis, clone COLF6621.
NM_004599	SREBF2	NP_004590	Homo sapiens sterol regulatory element binding transcription factor 2 (SREBF2), mRNA.
NM_005968	HNRPM	NP_005959	Homo sapiens heterogeneous nuclear ribonucleoprotein M (HNRPM), transcript variant 1, mRNA.
BC000138	HNRPM	AAH00138	Homo sapiens heterogeneous nuclear ribonucleoprotein M, transcript variant 1, mRNA (cDNA clone MGC:5136 IMAGE:2900532), complete cds.

Figure 19 (1)

GenBank Accession for mRNA	Gene Symbol	GenBank Accession for Protein	Nucleotide Sequence Description
NM_004992	MECP2	NP_004983	Homo sapiens methyl CpG binding protein 2 (Rett syndrome) (MECP2), mRNA.
NM_001714	BICD1	NP_001705	Homo sapiens Bicaudal D homolog 1 (Drosophila) (BICD1), mRNA.
NM_015409	EP400	NP_056224	Homo sapiens E1A binding protein p400 (EP400), mRNA.
BC007052	HNRPC	AAH07052	Homo sapiens heterogeneous nuclear ribonucleoprotein C (C1/C2), mRNA (cDNA clone MGC:12469 IMAGE:3686841), complete cds.
NM_012426	SF3B3	NP_036558	Homo sapiens splicing factor 3b, subunit 3, 130kDa (SF3B3), mRNA.
NM_003016	SFRS2	NP_003007	Homo sapiens splicing factor, arginine/serine-rich 2 (SFRS2), mRNA.
NM_002694	POLR2C	NP_002685	Homo sapiens polymerase (RNA) II (DNA directed) polypeptide C, 33kDa (POLR2C), transcript variant alpha, mRNA.
NM_002197	ACO1	NP_002188	Homo sapiens aconitase 1, soluble (ACO1), mRNA.
AF075000	H_YH95C04.1	AAC28457	Homo sapiens full length insert cDNA YH95C04.
BC002395	SF3A3	AAH02395	Homo sapiens splicing factor 3a, subunit 3, 60kDa, mRNA (cDNA clone MGC:8445 IMAGE:2821350), complete cds.
XM_056568	LOC147774	XP_056568	Homo sapiens similar to KH-type splicing regulatory protein (FUSE binding protein 2) (H. sapiens) (LOC147774), mRNA.
_004846	EIF4EL3	NP_004837	Homo sapiens eukaryotic translation initiation factor 4E-like 3 (EIF4EL3), mRNA.
_005463	HNRPDL	NP_005454	Homo sapiens heterogeneous nuclear ribonucleoprotein D-like (HNRPDL), transcript variant 1, mRNA.
_067844	LOC132430	XP_067844	Homo sapiens similar to Polyadenylate-binding protein 4 (Poly(A)-binding protein 4) (PABP 4) (Inducible poly(A)-binding protein) (iPABP) (Activated-platelet protein-1) (APP-1) (LOC132430), mRNA.
_006112	PPIE	NP_006103	Homo sapiens peptidylprolyl isomerase E (cyclophilin E) (PPIE), transcript variant 1, mRNA.
_017840	MRPL16	NP_060310	Homo sapiens mitochondrial ribosomal protein L16 (MRPL16), nuclear gene encoding mitochondrial protein, mRNA.
_030621	DICER1	NP_085124	Homo sapiens Dicer1, Dcr-1 homolog (Drosophila) (DICER1), transcript variant 2, mRNA.
_004397	DDX6	NP_004388	Homo sapiens DEAD (Asp-Glu-Ala-Asp) box polypeptide 6 (DDX6), mRNA.
NM_002111	HD	NP_002102	Homo sapiens huntingtin (Huntington disease) (HD), mRNA.
AL021546	SFRS9	CAA16498	Human DNA sequence from clone XX-15E1 on chromosome 12, complete sequence.
NM_033501	TRERF1	NP_277036	Homo sapiens transcriptional regulating factor 1 (TRERF1), transcript variant 2, mRNA.
BC012090		AAH12090	Homo sapiens, Similar to heterogeneous nuclear ribonucleoprotein A3, clone MGC:20045 IMAGE:4661041, mRNA, complete cds.
NM_006546	IMP-1	NP_006537	Homo sapiens IGF-II mRNA-binding protein 1 (IMP-1), mRNA.
XM_068928	LOC134611	XP_068928	Homo sapiens similar to TAR DNA binding protein (LOC134611), mRNA.
NM_016381	TREX1	NP_057465	Homo sapiens three prime repair exonuclease 1 (TREX1), transcript variant 1, mRNA.
NM_017518	TREX2	NP_059988	Homo sapiens three prime repair exonuclease 2 (TREX2), transcript variant 5, mRNA.
NM_015646	RAP1B	NP_056461	Homo sapiens RAP1B, member of RAS oncogene family (RAP1B), mRNA.
NM_052840	BRUNOL6	NP_443072	Homo sapiens bruno-like 6, RNA binding protein (Drosophila) (BRUNOL6), mRNA.

Figure 19(2)

GenBank Accession for mRNA	Gene Symbol	GenBank Accession for Protein	Nucleotide Sequence Description
NM_001538	HSF4	NP_001529	Homo sapiens heat shock transcription factor 4 (HSF4), mRNA.
XM_063246	LOC122663	XP_063246	Homo sapiens LOC122663 (LOC122663), mRNA.
XM_063244	LOC122661	XP_063244	Homo sapiens similar to Nonsecretory ribonuclease precursor (Ribonuclease US) (Eosinophil-derived neurotoxin) (RNase Upl-2) (Ribonuclease 2) (RNase 2) (LOC122661), mRNA.
AW607076			PM0-HT0452-140100-002-e07 HT0452 Homo sapiens cDNA, mRNA sequence.
NM_016816	OAS1	NP_058132	Homo sapiens 2',5'-oligoadenylate synthetase 1, 40/46kDa (OAS1), transcript variant E18, mRNA.
NM_004175	SNRPD3	NP_004166	Homo sapiens small nuclear ribonucleoprotein D3 polypeptide 18kDa (SNRPD3), mRNA.
AB020657	KIAA0850	BAA74873	Homo sapiens mRNA for KIAA0850 protein, partial cds.
BC000595	DDX17	AAH00595	Homo sapiens DEAD (Asp-Glu-Ala-Asp) box polypeptide 17, mRNA (cDNA clone MGC:2030 IMAGE:3345982), complete cds.
XM_094158	LOC152994	XP_094158	Homo sapiens similar to splicing factor 3a, subunit 2, 66kD; Spliceosome protein SAP-62 (LOC152994), mRNA.
NM_007204	DDX20	NP_009135	Homo sapiens DEAD (Asp-Glu-Ala-Asp) box polypeptide 20 (DDX20), mRNA.
NM_006980	MTERF	NP_008911	Homo sapiens transcription termination factor, mitochondrial (MTERF), nuclear gene encoding mitochondrial protein, mRNA.
NM_006491	NOVA1	NP_006482	Homo sapiens neuro-oncological ventral antigen 1 (NOVA1), transcript variant 3, mRNA.
NM_032102	SRP46	NP_115285	Homo sapiens Splicing factor, arginine/serine-rich, 46kD (SRP46), mRNA.
F035940	MAGOH	AAC39606	Homo sapiens MAGOH mRNA, complete cds.
NM_066948	LOC139891	XP_066948	Homo sapiens similar to hypothetical protein BC011593 (LOC139891), mRNA.
NM_007165	SF3A2	NP_009096	Homo sapiens splicing factor 3a, subunit 2, 66kDa (SF3A2), mRNA.
NM_014223	NFYC	NP_055038	Homo sapiens nuclear transcription factor Y, gamma (NFYC), mRNA.
NM_093219	LOC170270	XP_093219	Homo sapiens similar to Heterogeneous nuclear ribonucleoprotein A3 homolog 2 (hnRNP A3(B)) (LOC170270), mRNA.
NM_002137	HNRPA2B1	NP_002128	Homo sapiens heterogeneous nuclear ribonucleoprotein A2/B1 (HNRPA2B1), transcript variant A2, mRNA.
AJ252060	TRABID	CAB64449	Homo sapiens mRNA for TRABID protein (TRABID gene).
NM_014977	ACINUS	NP_055792	Homo sapiens apoptotic chromatin condensation inducer in the nucleus (ACINUS), mRNA.
XM_094555	LOC167540	XP_094555	Homo sapiens similar to RIKEN cDNA C130020J04 (LOC167540), mRNA.
XM_065946	LOC130900	XP_065946	Homo sapiens similar to Heterogeneous nuclear ribonucleoprotein A1 (Helix-destabilizing protein) (Single-strand binding protein) (hnRNP core protein A1) (HDP-1) (Topoisomerase-inhibitor suppressed) (LOC130900), mRNA.
AF005068	BRCA1	AAB61673	Homo sapiens breast and ovarian cancer susceptibility protein splice variant (BRCA1) mRNA, complete cds.
NM_012469	C20orf14	NP_036601	Homo sapiens chromosome 20 open reading frame 14 (C20orf14), mRNA.
NM_004643	PABPN1	NP_004634	Homo sapiens poly(A) binding protein, nuclear 1 (PABPN1), mRNA.
NM_003325	HIRA	NP_003316	Homo sapiens HIR histone cell cycle regulation defective homolog A (S. cerevisiae) (HIRA), mRNA.

Figure 19(3)

GenBank Accession for mRNA	Gene Symbol	GenBank Accession for Protein	Nucleotide Sequence Description
NM_019038	TDRD4	NP_061911	Homo sapiens tudor domain containing 4 (TDRD4), mRNA.
NM_025065	RPF1	NP_079341	Homo sapiens RNA processing factor 1 (RPF1), mRNA.
NM_005877	SF3A1	NP_005868	Homo sapiens splicing factor 3a, subunit 1, 120kDa (SF3A1), mRNA.
NM_002138	HNRPD	NP_002129	Homo sapiens heterogeneous nuclear ribonucleoprotein D (AU-rich element RNA binding protein 1, 37kDa) (HNRPD), transcript variant 3, mRNA.
XM_058876	MGC49942	XP_058876	Homo sapiens hypothetical protein MGC49942 (MGC49942), mRNA.
NM_021976	RXRB	NP_068811	Homo sapiens retinoid X receptor, beta (RXRB), mRNA.
NM_003489	NRIP1	NP_003480	Homo sapiens nuclear receptor interacting protein 1 (NRIP1), mRNA.
M29916	RMRP		Human mitochondrial RNA-processing endoribonuclease RNA (mrp) gene; complete cds.
XM_066446	LOC139051	XP_066446	Homo sapiens similar to pol protein (LOC139051), mRNA.

Figure 19(4)

GenBank Accession for mRNA	Gene Symbol	GenBank Accession for Protein	Nucleotide Sequence Description
NM_007297	BRCA1	NP_009228	Homo sapiens breast cancer 1, early onset (BRCA1), transcript variant BRCA1-delta2-10, mRNA.
NM_022830	FLJ22347	NP_073741	Homo sapiens hypothetical protein FLJ22347 (FLJ22347), mRNA.
NM_018722	HSA404617	NP_061192	Homo sapiens BWRT protein (HSA404617), mRNA.
XM_058876	MGC49942	XP_058876	Homo sapiens hypothetical protein MGC49942 (MGC49942), mRNA.
NM_015698	T54	NP_056513	Homo sapiens T54 protein (T54), mRNA.
XM_060102	LOC126635	XP_060102	Homo sapiens LOC126635 (LOC126635), mRNA.
NM_013316	CNOT4	NP_037448	Homo sapiens CCR4-NOT transcription complex, subunit 4 (CNOT4), mRNA.
AB033019	KIAA1193	BAA86507	Homo sapiens mRNA for KIAA1193 protein, partial cds.
XM_067598	LOC131898	XP_067598	Homo sapiens similar to POLYADENYLATE-BINDING PROTEIN 2 (POLY(A) BINDING PROTEIN 2) (PABP 2) (LOC131898), mRNA.
NM_000937	POLR2A	NP_000928	Homo sapiens polymerase (RNA) II (DNA directed) polypeptide A, 220kDa (POLR2A), mRNA.
XM_087530	LOC152827	XP_087530	Homo sapiens similar to hypothetical protein FLJ20273 (LOC152827), mRNA.
M_047272	LOC92781	XP_047272	Homo sapiens similar to dJ309K20.4 (KIAA0765, putative brain nuclearly targeted protein (HRIHFB2091, RNA recognition motif (RNP, RRM or RBD domain) containing protein)) (LOC92781), mRNA.
M_090177	LOC160258	XP_090177	Homo sapiens similar to nuclear matrix protein NMP200 related to splicing factor PRP19 (H. sapiens) (LOC160258), mRNA.
J252060	TRABID	CAB64449	Homo sapiens mRNA for TRABID protein (TRABID gene).
M_007185	TNRC4	NP_009116	Homo sapiens trinucleotide repeat containing 4 (TNRC4), mRNA.
B036532	p53R2	BAA92493	Homo sapiens p53R2 gene for ribonucleotide reductase, exon 9 and complete cds.
M_005119	THRAP3	NP_005110	Homo sapiens thyroid hormone receptor associated protein 3 (THRAP3), mRNA.
M_013235	RNASE3L	NP_037367	Homo sapiens nuclear RNase III Drosha (RNASE3L), mRNA.
M_004175	SNRPD3	NP_004166	Homo sapiens small nuclear ribonucleoprotein D3 polypeptide 18kDa (SNRPD3), mRNA.
XM_066586	LOC139264	XP_066586	Homo sapiens similar to Con1 (LOC139264), mRNA.
NM_018122	FLJ10514	NP_060592	Homo sapiens hypothetical protein FLJ10514 (FLJ10514), mRNA.
NM_006540	NCOA2	NP_006531	Homo sapiens nuclear receptor coactivator 2 (NCOA2), mRNA.
BC004154	NR2F1	AAH04154	Homo sapiens nuclear receptor subfamily 2, group F, member 1, mRNA (cDNA clone MGC:2388 IMAGE:2824138), complete cds.
NM_006567	FARS1	NP_006558	Homo sapiens phenylalanine-tRNA synthetase 1 (mitochondrial) (FARS1), nuclear gene encoding mitochondrial protein, mRNA.
XM_086792	LOC150152	XP_086792	Homo sapiens similar to SPLICING FACTOR U2AF 35 KD SUBUNIT (U2 AUXILIARY FACTOR 35 KD SUBUNIT) (U2 SNRNP AUXILIARY FACTOR SMALL SUBUNIT) (LOC150152), mRNA.
AF084974	EXOI	AAD13754	Homo sapiens exonuclease I (EXOI) mRNA, complete cds.

Figure 20 (1)

GenBank Accession for mRNA	Gene Symbol	GenBank Accession for Protein	Nucleotide Sequence Description
XM_064113	LOC124380	XP_064113	Homo sapiens LOC124380 (LOC124380), mRNA.
NM_002904	RDBP	NP_002895	Homo sapiens RD RNA binding protein (RDBP), mRNA.
NM_005463	HNRPDL	NP_005454	Homo sapiens heterogeneous nuclear ribonucleoprotein D-like (HNRPDL), transcript variant 1, mRNA.
NM_003244	TGIF	NP_003235	Homo sapiens TGFB-induced factor (TALE family homeobox) (TGIF), transcript variant 4, mRNA.
XM_070603	LOC137784	XP_070603	Homo sapiens similar to ANTIGEN GOR (LOC137784), mRNA.
NM_018415	TRERF1	NP_060885	Homo sapiens transcriptional regulating factor 1 (TRERF1), transcript variant 3, mRNA.
XM_065361	LOC129715	XP_065361	Homo sapiens similar to tudor protein (LOC129715), mRNA.
NM_020158	RRP46	NP_064543	Homo sapiens exosome component Rrp46 (RRP46), mRNA.
NM_004343	CALR	NP_004334	Homo sapiens calreticulin (CALR), mRNA.
NM_006112	PPIE	NP_006103	Homo sapiens peptidylprolyl isomerase E (cyclophilin E) (PPIE), transcript variant 1, mRNA.
NM_005877	SF3A1	NP_005868	Homo sapiens splicing factor 3a, subunit 1, 120kDa (SF3A1), mRNA.
_001714	BICD1	NP_001705	Homo sapiens Bicaudal D homolog 1 (Drosophila) (BICD1), mRNA.
_002467	MYC	NP_002458	Homo sapiens v-myc myelocytomatosis viral oncogene homolog (avian) (MYC), mRNA.
_014663	JMJD2A	NP_055478	Homo sapiens jumonji domain containing 2A (JMJD2A), mRNA.
_001436	FBL	NP_001427	Homo sapiens fibrillarin (FBL), mRNA.
_019038	TDRD4	NP_061911	Homo sapiens tudor domain containing 4 (TDRD4), mRNA.

Figure 20(2)

GenBank Accession for mRNA	Gene Symbol	GenBank Accession for Protein	Nucleotide Sequence Description
NM_013302	EEF2K	NP_037434	Homo sapiens elongation factor-2 kinase (EEF2K), mRNA.
NM_017948	NOL8	NP_060418	Homo sapiens nucleolar protein 8 (NOL8), mRNA.
XM_089332	LOC149382	XP_089332	Homo sapiens similar to ribosomal protein L22 proprotein; 60S ribosomal protein L22; Epstein-Barr-encoded RNA-associated protein; Epstein-Barr virus small RNA-associated protein; EBER-associated protein; heparin-binding protein 15; heparin-binding protein HBp15... (LOC149382), mRNA.
AF001947	PRP3	AAC09069	Homo sapiens U4/U6-associated RNA splicing factor (PRP3) mRNA, complete cds.
AF062105	IGH	AAC18141	Homo sapiens clone 21u-19 immunoglobulin heavy chain variable region (IGH) mRNA, partial cds.
NM_004169	SHMT1	NP_004160	Homo sapiens serine hydroxymethyltransferase 1 (soluble) (SHMT1), transcript variant 1, mRNA.
NM_000992	RPL29	NP_000983	Homo sapiens ribosomal protein L29 (RPL29), mRNA.
XM_060808	LOC128072	XP_060808	Homo sapiens similar to Vigilin (High density lipoprotein-binding protein) (HDL-binding protein) (LOC128072), mRNA.
NM_003902	FUBP1	NP_003893	Homo sapiens far upstream element (FUSE) binding protein 1 (FUBP1), mRNA.
XM_084392	LOC142966	XP_084392	Homo sapiens region containing tudor; Ras homolog enriched in brain 2 (LOC142966), mRNA.
^F391283	SSA1	AAK76432	Homo sapiens 11p15.5 clone LOH11A, partial sequence.
M_003325	HIRA	NP_003316	Homo sapiens HIR histone cell cycle regulation defective homolog A (S. cerevisiae) (HIRA), mRNA.
M_070832	LOC138267	XP_070832	Homo sapiens similar to hypothetical protein (LOC138267), mRNA.
M_088257	LOC155435	XP_088257	Homo sapiens hypothetical protein LOC155435 (LOC155435), mRNA.
K021418			Homo sapiens cDNA FLJ11356 fis, clone HEMBA1000150, highly similar to Homo sapiens putative RNA helicase mRNA.
J252060	TRABID	CAB64449	Homo sapiens mRNA for TRABID protein (TRABID gene).
M_014852	KIAA0682	NP_055667	Homo sapiens KIAA0682 gene product (KIAA0682), mRNA.
M_005870	SAP18	NP_005861	Homo sapiens sin3-associated polypeptide, 18kDa (SAP18), mRNA.
NM_005587	MEF2A	NP_005578	Homo sapiens MADS box transcription enhancer factor 2, polypeptide A (myocyte enhancer factor 2A) (MEF2A), mRNA.
NM_016169	SUFU	NP_057253	Homo sapiens suppressor of fused homolog (Drosophila) (SUFU), mRNA.
XM_089062	LOC148866	XP_089062	Homo sapiens similar to HETEROGENEOUS NUCLEAR RIBONUCLEOPROTEIN A1 (HELIX-DESTABILIZING PROTEIN) (SINGLE-STRAND BINDING PROTEIN) (HNRNP CORE PROTEIN A1) (LOC148866), mRNA.
NM_004875	POLR1C	NP_004866	Homo sapiens polymerase (RNA) I polypeptide C, 30kDa (POLR1C), transcript variant 2, mRNA.
AF129756		AAD18092	Homo sapiens MSH55 gene, partial cds; and CLIC1, DDAH, G6b, G6c, G5b, G6d, G6e, G6f, BAT5, G5b, CSK2B, BAT4, G4, Apo M, BAT3, BAT2, AIF-1, 1C7, LST-1, LTB, TNF, and LTA genes, complete cds.
NM_014872	ZBTB5	NP_055687	Homo sapiens zinc finger and BTB domain containing 5 (ZBTB5), mRNA.

Figure 21 (1)

GenBank Accession for mRNA	Gene Symbol	GenBank Accession for Protein	Nucleotide Sequence Description
NM_015629	PRPF31	NP_056444	Homo sapiens PRP31 pre-mRNA processing factor 31 homolog (yeast) (PRPF31), mRNA.
NM_017921	NPL4	NP_060391	Homo sapiens hypothetical protein FLJ20657 (NPL4), mRNA.
NM_002534	OAS1	NP_002525	Homo sapiens 2',5'-oligoadenylate synthetase 1, 40/46kDa (OAS1), transcript variant E16, mRNA.
AF083441		AAD52028	Homo sapiens SUI1 isolog mRNA, complete cds.
AF026563	RBMII		Homo sapiens RBMII gene, exon 6.
NM_012330	MYST4	NP_036462	Homo sapiens MYST histone acetyltransferase (monocytic leukemia) 4 (MYST4), mRNA.
NM_003298	NR2C2	NP_003289	Homo sapiens nuclear receptor subfamily 2, group C, member 2 (NR2C2), mRNA.
XM_061319	LOC119177	XP_061319	Homo sapiens similar to HETEROGENEOUS NUCLEAR RIBONUCLEOPROTEIN A1 (HELIX-DESTABILIZING PROTEIN) (SINGLE-STRAND BINDING PROTEIN) (HNRNP CORE PROTEIN A1) (LOC119177), mRNA.
XM_091974	LOC147891	XP_091974	Homo sapiens similar to hypothetical protein DKFZp434I1930 (H. sapiens) (LOC147891), mRNA.
NM_032102	SRP46	NP_115285	Homo sapiens Splicing factor, arginine/serine-rich, 46kD (SRP46), mRNA.
NM_052879	LOC113251	NP_443111	Homo sapiens c-Mpl binding protein (LOC113251), transcript variant 1, mRNA.
M_019038	TDRD4	NP_061911	Homo sapiens tudor domain containing 4 (TDRD4), mRNA.
M_000991	RPL28	NP_000982	Homo sapiens ribosomal protein L28 (RPL28), mRNA.
M_006893	LGTN	NP_008824	Homo sapiens ligatin (LGTN), mRNA.
M_060102	LOC126635	XP_060102	Homo sapiens LOC126635 (LOC126635), mRNA.
M_025065	RPF1	NP_079341	Homo sapiens RNA processing factor 1 (RPF1), mRNA.
M_004774	PPARBP	NP_004765	Homo sapiens PPAR binding protein (PPARBP), mRNA.
M_022767	FLJ12484	NP_073604	Homo sapiens hypothetical protein FLJ12484 (FLJ12484), mRNA.
M_007165	SF3A2	NP_009096	Homo sapiens splicing factor 3a, subunit 2, 66kDa (SF3A2), mRNA.
M_068248	LOC133225	XP_068248	Homo sapiens similar to heterogeneous ribonuclear particle protein A1.beta - human (LOC133225), mRNA.
NM_004039	ANXA2	NP_004030	Homo sapiens annexin A2 (ANXA2), mRNA.

Figure 21(2)

GenBank Accession for mRNA	Gene Symbol	GenBank Accession for Protein	Nucleotide Sequence Description
NM_007375	TARDBP	NP_031401	Homo sapiens TAR DNA binding protein (TARDBP), mRNA.
NM_000978	RPL23	NP_000969	Homo sapiens ribosomal protein L23 (RPL23), mRNA.
NM_005035	POLRMT	NP_005026	Homo sapiens polymerase (RNA) mitochondrial (DNA directed) (POLRMT), nuclear gene encoding mitochondrial protein, mRNA.
NM_018723	A2BP1	NP_061193	Homo sapiens ataxin 2-binding protein 1 (A2BP1), transcript variant 4, mRNA.
NM_031274	TEX13A	NP_112564	Homo sapiens testis expressed sequence 13A (TEX13A), mRNA.
NM_019037	RRP41	NP_061910	Homo sapiens exosome complex exonuclease RRP41 (RRP41), mRNA.
NM_002938	RNF4	NP_002929	Homo sapiens ring finger protein 4 (RNF4), mRNA.
NM_016024	CGI-79	NP_057108	Homo sapiens CGI-79 protein (CGI-79), mRNA.
NM_000980	RPL18A	NP_000971	Homo sapiens ribosomal protein L18a (RPL18A), mRNA.
NM_005642	TAF7	NP_005633	Homo sapiens TAF7 RNA polymerase II, TATA box binding protein (TBP)-associated factor, 55kDa (TAF7), mRNA.
XM_094555	LOC167540	XP_094555	Homo sapiens similar to RIKEN cDNA C130020J04 (LOC167540), mRNA.
NM_020967	NCOA5	NP_066018	Homo sapiens nuclear receptor coactivator 5 (NCOA5), mRNA.
_006209	ENPP2	NP_006200	Homo sapiens ectonucleotide pyrophosphatase/phosphodiesterase 2 (autotaxin) (ENPP2), mRNA.
_015934	NOP5/NOP58	NP_057018	Homo sapiens nucleolar protein NOP5/NOP58 (NOP5/NOP58), mRNA.
_003170	SUPT6H	NP_003161	Homo sapiens suppressor of Ty 6 homolog (S. cerevisiae) (SUPT6H), mRNA.
_005772	RCL1	NP_005763	Homo sapiens RNA terminal phosphate cyclase-like 1 (RCL1), mRNA.
_063346	LOC122888	XP_063346	Homo sapiens similar to polypyrimidine-tract binding protein (LOC122888), mRNA.
026126	HNRPD	AAC23476	Homo sapiens heterogeneous nuclear ribonucleoprotein D (HNRPD) gene, complete cds.
_000989	RPL30	NP_000980	Homo sapiens ribosomal protein L30 (RPL30), mRNA.
267533		AAF78955	Homo sapiens CUG-binding protein LYLQ isoform mRNA, complete cds.
_004491	GRLF1	NP_004482	Homo sapiens glucocorticoid receptor DNA binding factor 1 (GRLF1), transcript variant 2, mRNA.
_005336	HDLBP	NP_005327	Homo sapiens high density lipoprotein binding protein (vigilin) (HDLBP), mRNA.
_001970	EIF5A	NP_001961	Homo sapiens eukaryotic translation initiation factor 5A (EIF5A), mRNA.
XM_062603	LOC121372	XP_062603	Homo sapiens similar to ITBA4 PROTEIN (H. sapiens) (LOC121372), mRNA.
XM_001524	LOC151173	XP_001524	Homo sapiens similar to TAR DNA-binding protein-43 (TDP-43) (LOC151173), mRNA.
XM_084392	LOC142966	XP_084392	Homo sapiens region containing tudor; Ras homolog enriched in brain 2 (LOC142966), mRNA.
NM_014281	SIAHBP1	NP_055096	Homo sapiens fuse-binding protein-interacting repressor (SIAHBP1), transcript variant 2, mRNA.
NM_016505	PS1D	NP_057589	Homo sapiens putative S1 RNA binding domain protein (PS1D), mRNA.
NM_004600	SSA2	NP_004591	Homo sapiens Sjogren syndrome antigen A2 (60kDa, ribonucleoprotein autoantigen SS-A/Ro) (SSA2), mRNA.
NM_003091	SNRPB	NP_003082	Homo sapiens small nuclear ribonucleoprotein polypeptides B and B1 (SNRPB), transcript variant 2, mRNA.
NM_006862	TDRKH	NP_006853	Homo sapiens tudor and KH domain containing (TDRKH), mRNA.
NM_015156	RCOR	NP_055971	Homo sapiens REST corepressor (RCOR), mRNA.

Figure 22 (1)

GenBank Accession for mRNA	Gene Symbol	GenBank Accession for Protein	Nucleotide Sequence Description
NM_018387	STRBP	NP_060857	Homo sapiens spermatid perinuclear RNA binding protein (STRBP), mRNA.
NM_003787	NOL4	NP_003778	Homo sapiens nucleolar protein 4 (NOL4), mRNA.
NM_001356	DDX3X	NP_001347	Homo sapiens DEAD (Asp-Glu-Ala-Asp) box polypeptide 3, X-linked (DDX3X), transcript variant 2, mRNA.
NM_012330	MYST4	NP_036462	Homo sapiens MYST histone acetyltransferase (monocytic leukemia) 4 (MYST4), mRNA.
NM_007367	RALY	NP_031393	Homo sapiens RNA binding protein (autoantigenic, hnRNP-associated with lethal yellow) (RALY), transcript variant 2, mRNA.
NM_005548	KARS	NP_005539	Homo sapiens lysyl-tRNA synthetase (KARS), mRNA.
NM_001436	FBL	NP_001427	Homo sapiens fibrillarin (FBL), mRNA.
NM_012279	JAZ	NP_036411	Homo sapiens double-stranded RNA-binding zinc finger protein JAZ (JAZ), mRNA.
NM_002296	LBR	NP_002287	Homo sapiens lamin B receptor (LBR), transcript variant 1, mRNA.
NM_001071	TYMS	NP_001062	Homo sapiens thymidylate synthetase (TYMS), mRNA.
XM_062601	LOC121365	XP_062601	Homo sapiens similar to RBM1 (LOC121365), mRNA.
NM_000982	RPL21	NP_000973	Homo sapiens ribosomal protein L21 (RPL21), mRNA.
_058819	MSI2	XP_058819	Homo sapiens musashi homolog 2 (Drosophila) (MSI2), mRNA.
_084625	LOC143763	XP_084625	Homo sapiens similar to coactivator activator (LOC143763), mRNA.
_000971	RPL7	NP_000962	Homo sapiens ribosomal protein L7 (RPL7), mRNA.
049523	HYPA	AAC27501	Homo sapiens huntingtin-interacting protein HYPA/FBP11 (HYPA) mRNA, partial cds.
_000990	RPL27A	NP_000981	Homo sapiens ribosomal protein L27a (RPL27A), mRNA.
_001031	RPS28	NP_001022	Homo sapiens ribosomal protein S28 (RPS28), mRNA.
_001021	RPS17	NP_001012	Homo sapiens ribosomal protein S17 (RPS17), mRNA.
_017993	FLJ10094	NP_060463	Homo sapiens hypothetical protein FLJ10094 (FLJ10094), mRNA.
I_003651	CSDA	NP_003642	Homo sapiens cold shock domain protein A (CSDA), mRNA.
I_001714	BICD1	NP_001705	Homo sapiens Bicaudal D homolog 1 (Drosophila) (BICD1), mRNA.
I_033360	KRAS2	NP_203524	Homo sapiens v-Ki-ras2 Kirsten rat sarcoma 2 viral oncogene homolog (KRAS2), transcript variant a, mRNA.
L13848	DDX9	AAB48855	Human RNA helicase A mRNA, complete cds.
BC004154	NR2F1	AAH04154	Homo sapiens nuclear receptor subfamily 2, group F, member 1, mRNA (cDNA clone MGC:2388 IMAGE:2824138), complete cds.
NM_016304	C15orf15	NP_057388	Homo sapiens chromosome 15 open reading frame 15 (C15orf15), mRNA.
NM_022551	RPS18	NP_072045	Homo sapiens ribosomal protein S18 (RPS18), mRNA.
NM_003244	TGIF	NP_003235	Homo sapiens TGFB-induced factor (TALE family homeobox) (TGIF), transcript variant 4, mRNA.
NM_003095	SNRPF	NP_003086	Homo sapiens small nuclear ribonucleoprotein polypeptide F (SNRPF), mRNA.
NM_003017	SFRS3	NP_003008	Homo sapiens splicing factor, arginine/serine-rich 3 (SFRS3), mRNA.
NM_033246	PML	NP_150249	Homo sapiens promyelocytic leukemia (PML), transcript variant 7, mRNA.
NM_003754	EIF3S5	NP_003745	Homo sapiens eukaryotic translation initiation factor 3, subunit 5 epsilon, 47kDa (EIF3S5), mRNA.

Figure 22 (2)

GenBank Accession for mRNA	Gene Symbol	GenBank Accession for Protein	Nucleotide Sequence Description
XM_012968	LOC151921	XP_012968	Homo sapiens similar to chromosome 20 open reading frame 14; putative mitochondrial outer membrane protein import receptor; similar to yeast pre-mRNA splicing factors, Prp1/Zer and Prp6 (LOC151921), mRNA.
NM_004593	SFRS10	NP_004584	Homo sapiens splicing factor, arginine/serine-rich 10 (transformer 2 homolog, Drosophila) (SFRS10), mRNA.
NM_017489	TERF1	NP_059523	Homo sapiens telomeric repeat binding factor (NIMA-interacting) 1 (TERF1), transcript variant 1, mRNA.
NM_020143	LOC56902	NP_064528	Homo sapiens putatative 28 kDa protein (LOC56902), mRNA.
XM_067072	LOC140098	XP_067072	Homo sapiens similar to RBM1 (LOC140098), mRNA.
XM_059656	LOC133522	XP_059656	Homo sapiens similar to PGC-1 related co-activator (LOC133522), mRNA.
X99302	pop1	CAA67684	H.sapiens mRNA for Pop1 protein.
AL080063	DKFZp564I052	CAB45694	Homo sapiens mRNA; cDNA DKFZp564I052 (from clone DKFZp564I052).
NM_006112	PPIE	NP_006103	Homo sapiens peptidylprolyl isomerase E (cyclophilin E) (PPIE), transcript variant 1, mRNA.
_005826	HNRPR	NP_005817	Homo sapiens heterogeneous nuclear ribonucleoprotein R (HNRPR), mRNA.
_003819	PABPC4	NP_003810	Homo sapiens poly(A) binding protein, cytoplasmic 4 (inducible form) (PABPC4), mRNA.
_003690	PRKRA	NP_003681	Homo sapiens protein kinase, interferon-inducible double stranded RNA dependent activator (PRKRA), mRNA.
_001488	TADA2L	NP_001479	Homo sapiens transcriptional adaptor 2 (ADA2 homolog, yeast)-like (TADA2L), transcript variant 1, mRNA.
_058653	LOC122651	XP_058653	Homo sapiens LOC122651 (LOC122651), mRNA.
_004953	EIF4G1	NP_004944	Homo sapiens eukaryotic translation initiation factor 4 gamma, 1 (EIF4G1), transcript variant 5, mRNA.
_088868	LOC163412	XP_088868	Homo sapiens LOC163412 (LOC163412), mRNA.
_021038	MBNL1	NP_066368	Homo sapiens muscleblind-like (Drosophila) (MBNL1), mRNA.
_017736	FLJ20274	NP_060206	Homo sapiens hypothetical protein FLJ20274 (FLJ20274), mRNA.
NM_006451	PAIP1	NP_006442	Homo sapiens poly(A) binding protein interacting protein 1 (PAIP1), transcript variant 1, mRNA.
NM_004501	HNRPU	NP_004492	Homo sapiens heterogeneous nuclear ribonucleoprotein U (scaffold attachment factor A) (HNRPU), transcript variant 2, mRNA.
NM_001412	EIF1A	NP_001403	Homo sapiens eukaryotic translation initiation factor 1A (EIF1A), mRNA.
AB014564	KIAA0664	BAA31639	Homo sapiens mRNA for KIAA0664 protein, partial cds.
D80007	KIAA0185	BAA11502	Homo sapiens KIAA0185 mRNA, complete cds.
NM_004184	WARS	NP_004175	Homo sapiens tryptophanyl-tRNA synthetase (WARS), mRNA.
NM_019038	TDRD4	NP_061911	Homo sapiens tudor domain containing 4 (TDRD4), mRNA.
NM_030621	DICER1	NP_085124	Homo sapiens Dicer1, Dcr-1 homolog (Drosophila) (DICER1), transcript variant 2, mRNA.
AF167570		AAD51099	Homo sapiens nuclear factor associated with dsRNA NFAR-2 mRNA, complete cds.
NM_005872	BCAS2	NP_005863	Homo sapiens breast carcinoma amplified sequence 2 (BCAS2), mRNA.

Figure 22 (3)

GenBank Accession for mRNA	Gene Symbol	GenBank Accession for Protein	Nucleotide Sequence Description
D82351		BAA11561	Human retropseudogene MSSP-1 DNA, complete cds.
NM_004990	MARS	NP_004981	Homo sapiens methionine-tRNA synthetase (MARS), mRNA.
NM_006842	SF3B2	NP_006833	Homo sapiens splicing factor 3b, subunit 2, 145kD (SF3B2), mRNA
NM_017840	MRPL16	NP_060310	Homo sapiens mitochondrial ribosomal protein L16 (MRPL16), nuclear gene encoding mitochondrial protein, mRNA

Figure 22(4)

Nucleotide GenBank Accession Number or Manufacturer Sequence ID	Gene Name or Manufacturer Probe Name	Protein Product GeneBank Accsssion Number or Manufacturer Sequence Reference	Description
AB000280	PHT1	BAA20489	Rattus norvegicus mRNA for peptide/histidine transporter, complete cds.
AB011679		BAA32736	Rattus norvegicus mRNA for class I beta-tubulin, complete cds.
AB017265		BAA82585	Rattus norvegicus gene for glycosylphosphatidylinositol anchor attachment 1 (GPAA1), partial cds.
AB018253		BAA76556	Rattus norvegicus mRNA for voltage-gated ca channel, complete cds.
AB045586	cnr5	BAB61764	Rattus norvegicus cnr5 mRNA for cadherin-related neuronal receptor 5, partial cds.
AB047324	TAT1	BAB55595	Rattus norvegicus TAT1 mRNA, complete cds.
AB054997		BAB62175	Rattus norvegicus mRNA for QKI, partial cds.
AF003187		AAB60895	Rattus norvegicus cocaine attenuated zinc-finger protein mRNA, partial cds.
AF022089		AAB82556	Rattus norvegicus guanine nucleotide binding protein gamma 4 subunit mRNA, partial cds.
AF022091		AAB82558	Rattus norvegicus guanine nucleotide binding protein gamma 12 subunit mRNA, partial cds.
AF028604	P2X2	AAC72286	Rattus norvegicus P2X2 purinoceptor isoform f (P2X2) mRNA, partial cds.
AF035952	Krp3a	AAB88700	Rattus norvegicus kinesin-related protein 3A (Krp3a) mRNA, partial cds.
AF050159	IRS-2	AAC05512	Rattus norvegicus insulin receptor substrate 2 (IRS-2) mRNA, partial cds.
AF061443	LGR4	AAC77910	Rattus norvegicus G protein-coupled receptor LGR4 (LGR4) mRNA, complete cds.
AF079162	ptc	AAC99398	Rattus norvegicus patched (ptc) mRNA, partial cds.
AF083418	IRS-2	AAC33346	Rattus norvegicus insulin receptor substrate-2 (IRS-2) mRNA, partial cds.
AF087674	IRS-2	AAC36726	Rattus norvegicus insulin receptor substrate 2 (IRS-2) mRNA, partial cds.
AF102262	beta1-4GT	AAD41721	Rattus norvegicus N-acetylglucosamine galactosyltransferase (beta1-4GT) mRNA, partial cds.
AF109644	CAR1	AAF01255	Rattus norvegicus coxsackie-adenovirus-receptor homolog (CAR1) mRNA, partial cds.
AF130341	MT1	AAG18471	Rattus norvegicus melatonin receptor (MT1) mRNA, partial cds.
AF136231		AAD33684	Rattus norvegicus caspase-2 mRNA, complete cds.
AF148323	APPILS	AAF73106	Rattus norvegicus aminopeptidase PILS (APPILS) mRNA, complete cds.
AF159049		AAF80364	Rattus norvegicus angiotensin II type 1A receptor associated protein mRNA, complete cds.
AF186469	TM6P1	AAF01324	Rattus norvegicus TM6P1 (TM6P1) mRNA, complete cds.
AF189261	Theta	AAF70382	Rattus norvegicus GABA-A receptor theta subunit (Theta) mRNA, partial cds.

Figure 23

Nucleotide GenBank Accession Number or Manufacturer Sequence ID	Gene Name or Manufacturer Probe Name	Protein Product GeneBank Accsssion Number or Manufacturer Sequence Reference	Description
AF195045		AAF28720	Rattus norvegicus TRC8 gene, partial cds.
AF200359	Uggt	AAF67072	Rattus norvegicus UDP-glucose glycoprotein:glucosyltransferase precursor (Uggt) mRNA, complete cds.
AF228043		AAF76422	Rattus norvegicus nuclear hormone receptor co-regulator/co-activator mRNA, partial cds.
AF239219	Pgt2	AAK15063	Rattus norvegicus prostaglandin transporter subtype 2 (Pgt2) mRNA, complete cds.
AF244920		AAF44715	Rattus norvegicus potassium channel regulatory factor mRNA, complete cds.
AF260582		AAK49395	Rattus norvegicus hippyragranin mRNA, complete cds.
AF268030		AAF72546	Rattus norvegicus copper transporter 1 mRNA, complete cds.
AF273024		AAF81796	Rattus norvegicus amino acid system A transporter mRNA, complete cds.
AF352172		AAK32708	Rattus norvegicus v-raf murine sarcoma viral oncogene B1-like protein mRNA, partial cds.
AF361239		AAK67316	Rattus norvegicus lysosomal amino acid transporter 1 mRNA, complete cds.
AF385409	Eif5a2	AAL40650	Rattus norvegicus eukaryotic translation initiation factor 5A isoform II (Eif5a2) gene, exons 2 and 3 and partial cds.
AF385833		AAK66567	Rattus norvegicus RAC1 mRNA, partial cds.
AF406814		AAK96221	Rattus norvegicus clone PLRR-4 polymorphic leucine-rich repeat protein mRNA, complete cds.
AF439397	Sip30	AAL35221	Rattus norvegicus SNAP25 interacting protein 30 (Sip30) mRNA, complete cds.
AF441118	Bnip3l	AAL32462	Rattus norvegicus BNIP3L protein (Bnip3l) mRNA, complete cds.
AF442357		AAL35353	Rattus norvegicus reticulon 3 protein isoform a mRNA, complete cds; alternatively spliced.
AJ131111	LANCL1	CAB63943	Rattus sp. mRNA lanthionine synthetase C-like protein 1 (LANCL1 gene).
AJ224156		CAA11853	Rattus norvegicus mRNA for ceramide glucosyltransferase.
AJ243395	scn3b	CAB76838	Rattus norvegicus mRNA for voltage-gated sodium channel beta-3 subunit.
AY012054	Zfx	AAG38797	Rattus norvegicus zinc finger protein ZFX (Zfx) gene, partial cds.
D14418	PP2A ARa	BAA21903	Rattus norvegicus PP2A ARa mRNA for A regulatory subunit of protein phosphatase 2A, partial cds.
D16479	RTP-beta	BAA03940	Rat mRNA for mitochondrial long-chain 3-ketoacyl-CoA thiolase beta-subunit of mitochondrial trifunctional protein, complete cds.
D17521	ClC-3	BAA04471	Rattus rattus ClC-3 mRNA for protein kinase C-regulated chloride channel, complete cds.

Figure 23

Nucleotide GenBank Accession Number or Manufacturer Sequence ID	Gene Name or Manufacturer Probe Name	Protein Product GeneBank Accsssion Number or Manufacturer Sequence Reference	Description
D25233		BAA04958	Rattus norvegicus mRNA for retinoblastoma protein, partial sequence.
J02934		AAA41856	Rat cAMP-dependent protein kinase type II regualatory subunit mRNA, 3' end.
J04963		AAA41104	Rat ecto-ATPase mRNA, complete cds.
L09752	VIN1	AAA41010	Rat cyclin D2 (VIN1) mRNA, complete cds.
L10639	ActRII	AAA40674	Rat activin type II receptor (ActRII) mRNA, 5' end of cds.
L12382		AAA40687	Rattus norvegicus ADP-ribosylation factor 3 mRNA, complete cds.
L22761	GATA-GT2	AAA16159	Rat DNA binding protein (GATA-GT2) mRNA, complete cds.
M18331		AAA41872	Rat protein kinase C epsilon subspecies.
M18769		AAA41196	Rat liver beta-galactoside alpha 2,6-sialyltransferase mRNA, complete cds.
M19042		AAA41626	Rat proviral Moloney murine leukemia mutant in594-2 DNA, partial cds.
M24353		AAA66457	Rattus norvegicus alpha-mannosidase II mRNA, partial cds.
M32973		AAA41639	Rat mitochondrial solute carrier protein mRNA, 5' end.
M34083		AAA79273	Rat lactogen receptor mRNA, complete cds.
M35965		AAA42089	Rat thyroglobulin (rTg-2) mRNA, complete cds.
M55292	trkB	AAA42280	Rat neural receptor protein-tyrosine kinase (trkB) mRNA, complete cds.
NM_012506	Atp1a3	NP_036638	Rattus norvegicus ATPase, Na+/K+ transporting, alpha 3 polypeptide (Atp1a3), mRNA.
NM_012551	Egr1	NP_036683	Rattus norvegicus early growth response 1 (Egr1), mRNA.
NM_012563	Gad2	NP_036695	Rattus norvegicus glutamate decarboxylase 2 (Gad2), mRNA.
NM_012569	Gls	NP_036701	Rattus norvegicus glutaminase (Gls), mRNA.
NM_012609	Nf1	NP_036741	Rattus norvegicus neurofibromatosis 1 (Nf1), mRNA.
NM_012637	Ptpn1	NP_036769	Rattus norvegicus protein tyrosine phosphatase, non-receptor type 1 (Ptpn1), mRNA.
NM_012649	Sdc4	NP_036781	Rattus norvegicus syndecan 4 (Sdc4), mRNA.
NM_012655	Sp1	NP_036787	Rattus norvegicus Sp1 transcription factor (Sp1), mRNA.
NM_012663	Vamp2	NP_036795	Rattus norvegicus vesicle-associated membrane protein 2 (Vamp2), mRNA.
NM_012713	Prkcb1	NP_036845	Rattus norvegicus protein kinase C, beta 1 (Prkcb1), mRNA.

Figure 23

Nucleotide GenBank Accession Number or Manufacturer Sequence ID	Gene Name or Manufacturer Probe Name	Protein Product GeneBank Accsssion Number or Manufacturer Sequence Reference	Description
NM_012794	Glycam1	NP_036926	Rattus norvegicus glycosylation dependent cell adhesion molecule 1 (Glycam1), mRNA.
NM_012799	Nmbr	NP_036931	Rattus norvegicus neuromedin B receptor (Nmbr), mRNA.
NM_012806	Mapk10	NP_036938	Rattus norvegicus mitogen activated protein kinase 10 (Mapk10), mRNA.
NM_012836	Cpd	NP_036968	Rattus norvegicus carboxypeptidase D (Cpd), mRNA.
NM_012863	Mist1	NP_036995	Rattus norvegicus muscle, intestine and stomach expression 1 (Mist1), mRNA.
NM_012879	Slc2a2	NP_037011	Rattus norvegicus solute carrier family 2, member 2 (Slc2a2), mRNA.
NM_012919	Cacna2d1	NP_037051	Rattus norvegicus calcium channel, voltage-dependent, alpha2/delta subunit 1 (Cacna2d1), mRNA.
NM_012948	Emd	NP_037080	Rattus norvegicus emerin (Emd), mRNA.
NM_012998	P4hb	NP_037130	Rattus norvegicus prolyl 4-hydroxylase, beta polypeptide (P4hb), mRNA.
NM_013029	Siat8c	NP_037161	Rattus norvegicus sialyltransferase 8 C (Siat8c), mRNA.
NM_013038	Stxbp1	NP_037170	Rattus norvegicus syntaxin binding protein 1 (Stxbp1), mRNA.
NM_013080	Ptprz1	NP_037212	Rattus norvegicus protein tyrosine phosphatase, receptor-type, Z polypeptide 1 (Ptprz1), mRNA.
NM_013087	Cd81	NP_037219	Rattus norvegicus CD 81 antigen (Cd81), mRNA.
NM_013123	Il1r1	NP_037255	Rattus norvegicus interleukin 1 receptor, type I (Il1r1), mRNA.
NM_013159	Ide	NP_037291	Rattus norvegicus insulin degrading enzyme (Ide), mRNA.
NM_013181	Prkar1a	NP_037313	Rattus norvegicus protein kinase, cAMP dependent regulatory, type I, alpha (Prkar1a), mRNA.
NM_016999	Cyp4b1	NP_058695	Rattus norvegicus cytochrome P450, subfamily 4B, polypeptide 1 (Cyp4b1), mRNA.
NM_017065	Gabrb3	NP_058761	Rattus norvegicus gamma-aminobutyric acid receptor, subunit beta 3 (Gabrb3), mRNA.
NM_017091	Pcsk1	NP_058787	Rattus norvegicus proprotein convertase subtilisin/kexin type 1 (Pcsk1), mRNA.
NM_017135	Ak4	NP_058831	Rattus norvegicus adenylate kinase 4 (Ak4), mRNA.
NM_017197	Cugbp2	NP_058893	Rattus norvegicus CUG triplet repeat,RNA-binding protein 2 (Cugbp2), mRNA.
NM_017206	Slc6a6	NP_058902	Rattus norvegicus solute carrier family 6, member 6 (Slc6a6), mRNA.
NM_017231	Pitpn	NP_058927	Rattus norvegicus phosphatidylinositol transfer protein (Pitpn), mRNA.
NM_017269	Ptprj	NP_058965	Rattus norvegicus protein tyrosine phosphatase, receptor type, J (Ptprj), mRNA.
NM_017322	Mapk9	NP_059018	Rattus norvegicus stress activated protein kinase alpha II (Mapk9), mRNA.

Figure 23

Nucleotide GenBank Accession Number or Manufacturer Sequence ID	Gene Name or Manufacturer Probe Name	Protein Product GeneBank Accsssion Number or Manufacturer Sequence Reference	Description
NM_017323	Tr4	NP_059019	Rattus norvegicus TR4 orphan receptor (Tr4), mRNA.
NM_017348	CHOT1	NP_059044	Rattus norvegicus choline transporter (CHOT1), mRNA.
NM_019142	Prkaa1	NP_062015	Rattus norvegicus protein kinase, AMP-activated, alpha 1 catalytic subunit (Prkaa1), mRNA.
NM_019166	Syngr1	NP_062039	Rattus norvegicus synaptogyrin 1 (Syngr1), mRNA.
NM_019182	Rnf4	NP_062055	Rattus norvegicus ring finger protein 4 (Rnf4), mRNA.
NM_019192	Sepp1	NP_062065	Rattus norvegicus selenoprotein P, plasma, 1 (Sepp1), mRNA.
NM_019195	Cd47	NP_062068	Rattus norvegicus integrin-associated protein (Cd47), mRNA.
NM_019248	Ntrk3	NP_062121	Rattus norvegicus neural receptor protein-tyrosine kinase (Ntrk3), mRNA.
NM_019275	Madh4	NP_062148	Rattus norvegicus MAD homolog 4 (Drosophila) (Madh4), mRNA.
NM_019354	Ucp2	NP_062227	Rattus norvegicus uncoupling protein 2 (Ucp2), mRNA.
NM_019367	Ppt2	NP_062240	Rattus norvegicus palmitoyl-protein thioesterase 2 (Ppt2), mRNA.
NM_019377	Ywhab	NP_062250	Rattus norvegicus tyrosine 3-monooxgenase/tryptophan 5 monooxgenase activation protein, beta polypeptide (Ywhab), mRNA.
NM_021594	LOC59114	NP_067605	Rattus norvegicus ERM-binding phosphoprotein (LOC59114), mRNA.
NM_021597	Gerp95	NP_067608	Rattus norvegicus GERp95 (Gerp95), mRNA.
NM_021671	LOC59303	NP_067703	Rattus norvegicus db83 (LOC59303), mRNA.
NM_021680	Nxph4	NP_067712	Rattus norvegicus neurexophilin 4 (Nxph4), mRNA.
NM_021682	LOC59318	NP_067714	Rattus norvegicus kilon (LOC59318), mRNA.
NM_021851	Lin7c	NP_068623	Rattus norvegicus lin-7-C (Lin7c), mRNA.
NM_022005	Fxyd6	NP_071288	Rattus norvegicus FXYD domain-containing ion transport regulator 6 (Fxyd6), mRNA.
NM_022208	Gtf2a1	NP_071544	Rattus norvegicus general transcription factor 2a, 1 (Gtf2a1), mRNA.
NM_022223	Fgf14	NP_071559	Rattus norvegicus fibroblast growth factor 14 (Fgf14), mRNA.
NM_022231	Birc4	NP_071567	Rattus norvegicus baculoviral IAP repeat-containing 4 (Birc4), mRNA.
NM_022386	Mafg	NP_071781	Rattus norvegicus v-maf musculoaponeurotic fibrosarcoma (avian) oncogene family, protein G (Mafg), mRNA.

Figure 23

Nucleotide GenBank Accession Number or Manufacturer Sequence ID	Gene Name or Manufacturer Probe Name	Protein Product GeneBank Accession Number or Manufacturer Sequence Reference	Description
NM_022387	Pafah1b2	NP_071782	Rattus norvegicus platelet-activating factor acetylhydrolase alpha 2 subunit (PAF-AH alpha 2) (Pafah1b2), mRNA.
NM_022396	Gng11	NP_071791	Rattus norvegicus guanine nucleotide binding protein gamma subunit 11 (Gng11), mRNA.
NM_022502	Ppt	NP_071947	Rattus norvegicus palmitoyl-protein thioesterase (Ppt), mRNA.
NM_022516	Ptb	NP_071961	Rattus norvegicus polypyrimidine tract binding protein (Ptb), mRNA.
NM_022522	Casp2	NP_071967	Rattus norvegicus caspase 2 (Casp2), mRNA.
NM_022548	PAG608	NP_071993	Rattus norvegicus p53-activated gene 608 (PAG608), mRNA.
M_022612	Bcl2l11	NP_072134	Rattus norvegicus BCL2-like 11 (apoptosis facilitator) (Bcl2l11), transcript variant 1, mRNA.
M_022619	Slc7a2	NP_072141	Rattus norvegicus solute carrier family 7, member 3 (Slc7a2), mRNA.
M_022673	Mecp2	NP_073164	Rattus norvegicus methyl CpG binding protein 2 (Mecp2), mRNA.
M_022799	Nucks	NP_073636	Rattus norvegicus nuclear ubiquitous casein kinase 2 (Nucks), mRNA.
M_022931	Nim3	NP_075220	Rattus norvegicus nim3 protein (Nim3), mRNA.
M_022950	C1galt1	NP_075239	Rattus norvegicus core1 UDP-galactose:N-acetylgalactosamine-alpha-R beta 1,3-galactosyltransferase (C1galt1) (C1galt1), mRNA
M_023095	Mgat5	NP_075583	Rattus norvegicus N-acetylglucosaminyltransferase V (Mgat5), mRNA.
M_023956	Gucy1a2	NP_076446	Rattus norvegicus soluble guanylyl cyclase alpha2 subunit (Gucy1a2), mRNA.
M_023977	Gmx33	NP_076467	Rattus norvegicus trans-Golgi protein GMx33 (Gmx33), mRNA.
NM_023991	Prkaa2	NP_076481	Rattus norvegicus protein kinase, AMP-activated, alpha 2 catalytic subunit (Prkaa2), mRNA.
NM_024132	Faah	NP_077046	Rattus norvegicus fatty acid amide hydrolase (Faah), mRNA.
NM_024139	Chp	NP_077053	Rattus norvegicus calcium binding protein p22 (Chp), mRNA.
NM_024158	Dck	NP_077072	Rattus norvegicus deoxycytidine kinase (Dck), mRNA.
NM_024368	Frk	NP_077344	Rattus norvegicus src related tyrosine kinase (Frk), mRNA.
NM_024370	Gabrg3	NP_077346	Rattus norvegicus GABA-alpha receptor gamma-3 subunit (Gabrg3), mRNA.
NM_024374	Mtpn	NP_077350	Rattus norvegicus myotrophin (Mtpn), mRNA.
NM_030586	omb5	NP_085075	Rattus norvegicus cytochrome b5, outer mitochondrial membrane isoform (omb5), mRNA.

Figure 23

Nucleotide GenBank Accession Number or Manufacturer Sequence ID	Gene Name or Manufacturer Probe Name	Protein Product GeneBank Accsssion Number or Manufacturer Sequence Reference	Description
NM_030829	Gprk5	NP_110456	Rattus norvegicus G protein-coupled receptor kinase 5 (Gprk5), mRNA.
NM_030835	RAMP4	NP_110462	Rattus norvegicus ribosome associated membrane protein 4 (RAMP4), mRNA.
NM_030849	Bmpr1a	NP_110476	Rattus norvegicus bone morphogenetic protein receptor, type 1A (Bmpr1a), mRNA.
NM_030873	Pfn2	NP_110500	Rattus norvegicus profilin II (Pfn2), mRNA.
NM_030991	Snap25	NP_112253	Rattus norvegicus synaptosomal-associated protein (Snap25), mRNA.
NM_031011	Amd1	NP_112273	Rattus norvegicus S-adenosylmethionine decarboxylase 1 (Amd1), mRNA.
NM_031031	Gatm	NP_112293	Rattus norvegicus glycine amidinotransferase (L-arginine:glycine amidinotransferase) (Gatm), mRNA.
NM_031034	Gna12	NP_112296	Rattus norvegicus guanine nucleotide binding protein, alpha 12 (Gna12), mRNA.
NM_031036	Gnaq	NP_112298	Rattus norvegicus heterotrimeric guanine nucleotide-binding protein alpha q subunit (Gnaq), mRNA.
NM_031049	Lss	NP_112311	Rattus norvegicus 2,3-oxidosqualene: lanosterol cyclase (Lss), mRNA.
NM_031057	Mmsdh	NP_112319	Rattus norvegicus methylmalonate semialdehyde dehydrogenase gene (Mmsdh), mRNA.
NM_031061	Musk	NP_112323	Rattus norvegicus muscle, skeletal, receptor tyrosine kinase (Musk), mRNA.
NM_031079	Pde2a	NP_112341	Rattus norvegicus phosphodiesterase 2A, cGMP-stimulated (Pde2a), mRNA.
NM_031081	Pdpk1	NP_112343	Rattus norvegicus 3-phosphoinositide dependent protein kinase-1 (Pdpk1), mRNA.
NM_031120	Ssr3	NP_112382	Rattus norvegicus TRAP-complex gamma subunit (Ssr3), mRNA.
NM_031123	Stc1	NP_112385	Rattus norvegicus stanniocalcin 1 (Stc1), mRNA.
NM_031143	Dgkz	NP_112405	Rattus norvegicus diacylglycerol kinase zeta (Dgkz), mRNA.
NM_031152	Rab11a	NP_112414	Rattus norvegicus RAB11a, member RAS oncogene family (Rab11a), mRNA.
NM_031344	Fads2	NP_112634	Rattus norvegicus fatty acid desaturase 2 (Fads2), mRNA.
NM_031346	Rod1	NP_112636	Rattus norvegicus regulator of differentiation (in S. pombe) 1 (Rod1), mRNA.
NM_031515	Kras2	NP_113703	Rattus norvegicus Kirsten rat sarcoma viral oncogene homologue 2 (active) (Kras2), mRNA.
NM_031521	Ncam1	NP_113709	Rattus norvegicus neural cell adhesion molecule 1 (Ncam1), mRNA.
NM_031528	Rara	NP_113716	Rattus norvegicus retinoic acid receptor, alpha (Rara), mRNA.
NM_031575	Akt3	NP_113763	Rattus norvegicus thymoma viral proto-oncogene 3 (Akt3), mRNA.
NM_031593	Sv2c	NP_113781	Rattus norvegicus synaptic vesicle protein 2C (Sv2c), mRNA.

Figure 23

Nucleotide GenBank Accession Number or Manufacturer Sequence ID	Gene Name or Manufacturer Probe Name	Protein Product GeneBank Accsssion Number or Manufacturer Sequence Reference	Description
NM_031604	Atp6n1a	NP_113792	Rattus norvegicus ATPase, H+ transporting, lysosomal noncatalytic accessory protein 1a (Atp6n1a), mRNA.
NM_031605	Cyp4a12	NP_113793	Rattus norvegicus cytochrome P450, 4a12 (Cyp4a12), mRNA.
NM_031615	Znf148	NP_113803	Rattus norvegicus zinc finger protein 148 (Znf148), mRNA.
NM_031726	Scamp5	NP_113914	Rattus norvegicus secretory carrier membrane protein 5 (Scamp5), mRNA.
NM_031751	Shank1	NP_113939	Rattus norvegicus Shank1 (Shank1), mRNA.
NM_031755	Ceacam1	NP_113943	Rattus norvegicus carcinoembryonic antigen-related cell adhesion molecule 1 (Ceacam1), mRNA.
NM_031757	Mmp24	NP_113945	Rattus norvegicus matrix metalloproteinase 24 (membrane-inserted) (Mmp24), mRNA.
NM_031785	Atp6s1	NP_113973	Rattus norvegicus ATPase, H+ transporting, lysosomal (vacuolar proton pump), subunit 1 (Atp6s1), mRNA.
NM_031787	Hipk3	NP_113975	Rattus norvegicus homeodomain-interacting protein kinase 3 (Hipk3), mRNA.
NM_031812	Cd164	NP_114000	Rattus norvegicus CD164 antigen (Cd164), mRNA.
NM_031818	Clic4	NP_114006	Rattus norvegicus chloride intracellular channel 4 (Clic4), mRNA.
NM_031828	Kcnma1	NP_114016	Rattus norvegicus potassium large conductance calcium-activated channel, subfamily M, alpha member 1 (Kcnma1), mRNA.
NM_031841	Scd2	NP_114029	Rattus norvegicus stearoyl-Coenzyme A desaturase 2 (Scd2), mRNA.
NM_031986	Sdcbp	NP_114192	Rattus norvegicus syntenin (Sdcbp), mRNA.
NM_032080	Gsk3b	NP_114469	Rattus norvegicus glycogen synthase kinase 3 beta (Gsk3b), mRNA.
NM_032084	Chn2	NP_114473	Rattus norvegicus chimerin (chimaerin) 2 (Chn2), mRNA.
NM_033376	Kcnk3	NP_203694	Rattus norvegicus potassium channel, subfamily K, member 3 (Kcnk3), mRNA.
NM_052801	Vhl	NP_434688	Rattus norvegicus von Hippel-Lindau syndrome homolog (Vhl), mRNA.
NM_053308	Fkbp2	NP_445760	Rattus norvegicus FK506 binding protein 2 (Fkbp2), mRNA.
NM_053342	Idax	NP_445794	Rattus norvegicus inhibitor of the Dvl and Axin complex (Idax), mRNA.
NM_053352	Rdc1	NP_445804	Rattus norvegicus chemokine orphan receptor 1 (Rdc1), mRNA.
NM_053379	Dcx	NP_445831	Rattus norvegicus doublecortin (Dcx), mRNA.
NM_053407	Asah	NP_445859	Rattus norvegicus N-acylsphingosine amidohydrolase (acid ceramidase) (Asah), mRNA.
NM_053424	Slc4a4	NP_445876	Rattus norvegicus solute carrier family 4, member 4 (Slc4a4), mRNA.

Figure 23

Nucleotide GenBank Accession Number or Manufacturer Sequence ID	Gene Name or Manufacturer Probe Name	Protein Product GeneBank Accsssion Number or Manufacturer Sequence Reference	Description
NM_053442	Slc7a8	NP_445894	Rattus norvegicus solute carrier family 7 (cationic amino acid transporter, y+ system), member 8 (Slc7a8), mRNA.
NM_053445	Fads1	NP_445897	Rattus norvegicus fatty acid desaturase 1 (Fads1), mRNA.
NM_053465	Fut9	NP_445917	Rattus norvegicus fucosyltransferase 9 (alpha (1,3) fucosyltransferase) (Fut9), mRNA.
NM_053467	Tmp21	NP_445919	Rattus norvegicus integral membrane protein Tmp21-I (p23) (Tmp21), mRNA.
NM_053472	Cox4b	NP_445924	Rattus norvegicus cytochrome c oxidase, subunit 4b (Cox4b), mRNA.
NM_053486	Kif3c	NP_445938	Rattus norvegicus kinesin family member 3C (Kif3c), mRNA.
NM_053494	Slc2a8	NP_445946	Rattus norvegicus solute carrier family 2, (facilitated glucose transporter) member 8 (Slc2a8), mRNA.
NM_053502	Abcg1	NP_445954	Rattus norvegicus ATP-binding cassette, sub-family G (WHITE), member 1 (Abcg1), mRNA.
NM_053565	Cish3	NP_446017	Rattus norvegicus cytokine inducible SH2-containing protein 3 (Cish3), mRNA.
NM_053578	Atp6k	NP_446030	Rattus norvegicus vacuolar proton-ATPase subunit M9.2 (Atp6k), mRNA.
NM_053589	Rab14	NP_446041	Rattus norvegicus GTPase Rab14 (Rab14), mRNA.
NM_053646	Asah2	NP_446098	Rattus norvegicus N-acylsphingosine amidohydrolase 2 (Asah2), mRNA.
NM_053714	Ank	NP_446166	Rattus norvegicus progressive ankylosis (Ank), mRNA.
NM_053722	Clasp2	NP_446174	Rattus norvegicus CLIP-associating protein 2 (Clasp2), mRNA.
NM_053770	Argbp2	NP_446222	Rattus norvegicus Arg/Abl-interacting protein ArgBP2 (Argbp2), mRNA.
NM_053794	Prkwnk1	NP_446246	Rattus norvegicus protein kinase, lysine deficient 1 (Prkwnk1), mRNA.
NM_053798	Sacm1l	NP_446250	Rattus norvegicus SAC1 (supressor of actin mutations 1, homolog)-like (S. cerevisiae) (Sacm1l), mRNA.
NM_053863	Slc28a1	NP_446315	Rattus norvegicus solute carrier family 28 (sodium-coupled nucleoside transporter), member 1 (Slc28a1), mRNA.
NM_053886	Lman1	NP_446338	Rattus norvegicus lectin, mannose-binding, 1 (Lman1), mRNA.
NM_053891	Cdk5r	NP_446343	Rattus norvegicus cyclin-dependent kinase 5, regulatory subunit 1 (p35) (Cdk5r), mRNA.
NM_053952	Nup155	NP_446404	Rattus norvegicus nucleoporin 155kD (Nup155), mRNA.
NM_054000	Kcnb2	NP_446452	Rattus norvegicus potassium voltage gated channel, Shab-related subfamily, member 2 (Kcnb2), mRNA.
NM_057098	Tcea2	NP_476439	Rattus norvegicus transcription elongation factor A2 (Tcea2), mRNA.

Figure 23

Nucleotide GenBank Accession Number or Manufacturer Sequence ID	Gene Name or Manufacturer Probe Name	Protein Product GeneBank Accsssion Number or Manufacturer Sequence Reference	Description
NM_057132	Arha2	NP_476473	Rattus norvegicus plysia ras-related homolog A2 (Arha2), mRNA.
NM_057148	2-Sep	NP_476489	Rattus norvegicus septin 2 (Sept2), mRNA.
NM_057186	Hadhsc	NP_476534	Rattus norvegicus L-3-hydroxyacyl-Coenzyme A dehydrogenase, short chain (Hadhsc), mRNA.
NM_057210	Sv2a	NP_476558	Rattus norvegicus synaptic vesicle glycoprotein 2 a (Sv2a), mRNA.
NM_080577	Npl4	NP_542144	Rattus norvegicus homolog of yeast nuclear protein localization 4 (Npl4), mRNA.
S61973		AAB20211	Rattus sp. NMDA receptor glutamate-binding subunit mRNA, complete cds.
S73608	AGR9	AAB31153	AGR9=G protein-coupled receptor [rats, aortic vascular smooth muscle cells, mRNA, 1601 nt].
U07795	rap1B	AAA92787	Rattus norvegicus Rap1B mRNA, complete cds.
U15408		AAA81005	Rattus norvegicus plasma membrane Ca2+-ATPase isoform 4 mRNA, complete cds and alternatively spliced variations.
U21116		AAA96350	Rattus norvegicus rbSec1B mRNA, complete cds.
U31815	ROB2	AAA89157	Rattus norvegicus calcium channel alpha-1C subunit (ROB2) mRNA, partial cds.
U39572		AAD10400	Rattus norvegicus phosphatidylinositol 4-kinase mRNA, complete cds.
U40188	DN-7	AAC53201	Rattus norvegicus neuronal cell death related gene in neuron -7 (DN-7) mRNA, complete cds.
U41183	GHRH	AAC53041	Rattus norvegicus placental pre-progrowth hormone-releasing hormone (GHRH) mRNA, complete cds.
U41853	ORP150	AAB05672	Rattus norvegicus 150 kDa oxygen regulated protein (ORP150) mRNA, complete cds.
U53927		AAC52813	Rattus norvegicus brain astroglial high-affinity cationic amino acid transporter RCAT2 mRNA, partial cds.
U56261		AAA99825	Rattus norvegicus SNAP-25a mRNA, partial cds.
U61772	NF2	AAC13318	Rattus norvegicus merlin (NF2) mRNA, partial cds.
U67995		AAB39620	Rattus norvegicus stearyl-CoA desaturase 2 mRNA, partial cds.
U76997		AAB19066	Rattus norvegicus insulin-regulated membrane aminopeptidase IRAP mRNA, complete cds.
U77583	CKIaL	AAB19228	Rattus norvegicus casein kinase I alpha L (CKIaL) mRNA, complete cds.
U78090		AAC34249	Rattus norvegicus potassium channel regulator 1 mRNA, complete cds.
U78116	AZF5	AAB36788	Rattus norvegicus zinc finger protein 5 (AZF5) mRNA, partial cds.
U90215		AAB49989	Rattus norvegicus polysialyltransferase mRNA, partial cds.

Claim 23

Nucleotide GenBank Accession Number or Manufacturer Sequence ID	Gene Name or Manufacturer Probe Name	Protein Product GeneBank Accsssion Number or Manufacturer Sequence Reference	Description
X05472	ORF 3	CAA29033	Rat 2.4 kb repeat DNA right terminal region.
X53261		CAA37350	R.norvegicus mRNA for protein kinase A catalytic subunit.
X56747		CAA40069	Rat mRNA for fetal intestinal lactase-phlorizin hydrolase precursor, partial.
X60370		CAC16162	R.norvegicus mRNA for microtubule associated protein IB.
X60790	PYBP2	CAA43203	Rat PYBP2 mRNA for pyrimidine binding protein 2.
X64600	tgn41	CAA45884	R.norvegicus mRNA for the trans Golgi network specific integral membrane protein TGN41.
X80029	hem2	CAA56333	R.norvegicus Hem-2 mRNA.
X89963	TSP-4	CAA62002	R.norvegicus mRNA TSP-4 protein.
Y13336	DAD-1	CAA73780	Rattus norvegicus DAD-1 gene.
Y16774	Dri 27/ZnT4	CAA76372	Rattus norvegicus mRNA for Dri 27/ZnT4 protein, complete CDS.
Z18877		CAA79317	R.norvegicus mRNA for 2'5' oligoadenylate synthetase.
Z21935		CAA79929	R.norvegicus protein kinase rMNK2.
NM_023986	Temo	NP_076476	Rattus norvegicus TEMO (Temo), mRNA.
RATTUS00016	mwgrat10K#6143	u10860	u10860_1 guanosine 5'-monophosphate synthetase - homo sapiens expression: heart strains: sprague_dawley wistar_kyoto gbp
RATTUS00092	mwgrat10K#6206	bc014875	bc014875_1 unknown protein for mgc:6920 - mus musculus expression: liver heart brain kidney strains: shrsp sprague_dawley wistar_kyoto gbp
RATTUS00129	mwgrat10K#6238	q9hcc0	non-biotin containing subunit of 3-methylcrotonyl-coa carboxylase ec 6.4.1.4 expression: heart kidney strains: shrsp wistar_kyoto trembl
RATTUS00221	mwgrat10K#6320	bc003290	bc003290_1 cyclin i - mus musculus expression: kidney brain heart strains: shrsp sprague_dawley wistar_kyoto gbp
RATTUS00223	mwgrat10K#6321	q9p1l0	pro1038 expression: liver heart kidney strains: shrsp sprague_dawley wistar_kyoto trembl
RATTUS00276	mwgrat10K#8728	q9qz87	oda-8s protein; kidney expression: brain heart strains: sprague_dawley wistar_kyoto trembl
RATTUS00284	mwgrat10K#6373	ak008492	ak008492_1 riken full-length enriched library, clone:2010300f21 - mus musculus; heart kidney shrsp trembl o75319 pir1 ec 3.1.3.4 expression: brain strains: wistar_kyoto gbp

Figure 23

Nucleotide GenBank Accession Number or Manufacturer Sequence ID	Gene Name or Manufacturer Probe Name	Protein Product GeneBank Accsssion Number or Manufacturer Sequence Reference	Description
RATTUS00285	mwgrat10K#6374	af411608	af411608_1 n4wbp5a nedd4 ww domain-binding protein 5a - mus musculus expression: liver heart brain strains: shrsp sprague_dawley wistar_kyoto gbp
RATTUS00379	mwgrat10K#6453	q9gzu0	hypothetical 27.1 kda protein cdna flj12619 fis, clone nt2rm4001682 expression: liver brain heart strains: sprague_dawley wistar_kyoto trembl
RATTUS00410	mwgrat10K#6481	bc006847	bc006847_1 riken cdna 0610013i17 gene - mus musculus expression: liver heart strains: shrsp sprague_dawley wistar_kyoto gbp
RATTUS00415	mwgrat10K#6485	q9wvd5	ornithine transporter expression: liver heart kidney strains: shrsp sprague_dawley wistar_kyoto trembl
RATTUS00434	mwgrat10K#6501	q9h3n4	cisplatin resistance related protein crr9p expression: brain heart strains: shrsp sprague_dawley wistar_kyoto trembl
RATTUS00437	mwgrat10K#6503	bc014808	bc014808_1 proline rich protein expressed in brain - mus musculus expression: liver heart brain kidney strains: shrsp sprague_dawley wistar_kyoto gbp
RATTUS00451	mwgrat10K#6516	q9han2	pumilio 2; heart wistar_kyoto trembl q9erc7 expression: liver brain strains: shrsp sprague_dawley trembl
RATTUS00521	mwgrat10K#6575	ak009646	ak009646_1 riken full-length enriched library, clone:2310036d22 - mus musculus expression: liver heart brain strains: shrsp wistar_kyoto gbp
RATTUS00525	mwgrat10K#6579	af237619	af237619_1 dual specificity phosphatase ts-dsp2 - mus musculus expression: heart strains: shrsp wistar_kyoto gbp
RATTUS00526	mwgrat10K#6580	ak009743	ak009743_1 riken full-length enriched library, clone:2310042b03 - mus musculus expression: heart brain strains: shrsp sprague_dawley wistar_kyoto gbp
RATTUS00530	mwgrat10K#6584	q9nzj7	mitochondrial carrier homolog 1 isoform b expression: brain kidney strains: shrsp trembl
RATTUS00553	mwgrat10K#6606	q9h5j2	cdna: flj23389 fis, clone hep17027 expression: heart brain strains: sprague_dawley wistar_kyoto trembl
RATTUS00575	mwgrat10K#6624	q9jk95	p53 apoptosis-associated target expression: liver kidney heart strains: shrsp sprague_dawley wistar_kyoto trembl
RATTUS00704	mwgrat10K#6738	bc010856	bc010856_1 unknown protein for mgc:9160 - homo sapiens expression: brain strains: sprague_dawley wistar_kyoto gbp

Figure 23

Nucleotide GenBank Accession Number or Manufacturer Sequence ID	Gene Name or Manufacturer Probe Name	Protein Product GeneBank Accsssion Number or Manufacturer Sequence Reference	Description
RATTUS00794	mwgrat10K#6816	ak007469	ak007469_1 riken full-length enriched library, clone:1810013b01 - mus musculus expression: liver brain kidney strains: shrsp sprague_dawley wistar_kyoto gbp
RATTUS00848	mwgrat10K#6864	x61585	x61585_1 polynucleotide adenylyltransferase - bos taurus expression: liver heart kidney strains: shrsp wistar_kyoto gbp
RATTUS00867	mwgrat10K#6879	o95205	zinc finger protein expression: brain strains: shrsp sprague_dawley trembl
RATTUS00868	mwgrat10K#6880	bc006778	bc006778_1 unknown protein for image:3589064 - mus musculus expression: brain strains: shrsp sprague_dawley wistar_kyoto g
ATTUS00870	mwgrat10K#6881	q83380	envelope protein expression: liver brain strains: shrsp sprague_dawley wistar_kyoto trembl
ATTUS00904	mwgrat10K#6910	q9p1s0	hdckb03p fragment expression: brain strains: shrsp wistar_kyoto trembl
ATTUS00937	mwgrat10K#6941	q9ulf5	kiaa1265 protein fragment expression: brain strains: sprague_dawley wistar_kyoto trembl
ATTUS01071	mwgrat10K#7054	bc003862	bc003862_1 transmembrane 9 superfamily member 2 - mus musculus expression: liver heart kidney brain strains: shrsp sprague_dawley wistar_kyoto gbp
ATTUS01093	mwgrat10K#7071	q9y6r2	embryonic lung protein expression: liver brain heart strains: shrsp sprague_dawley wistar_kyoto trembl
ATTUS01148	mwgrat10K#7121	l10426	l10426_1 er81 ets-related protein - mus musculus expression: brain strains: sprague_dawley wistar_kyoto gbp
ATTUS01170	mwgrat10K#7138	ak020910	ak020910_1 riken full-length enriched library, clone:a930030i01 - mus musculus expression: brain strains: shrsp sprague_dawley wistar_kyoto gbp
RATTUS01205	mwgrat10K#7167	ak006207	ak006207_1 riken full-length enriched library, clone:1700021i06 - mus musculus expression: liver heart brain strains: shrsp sprague_dawley wistar_kyoto gbp
RATTUS01221	mwgrat10K#7181	aj278133	aj278133_1 erd2.2 putative kdel receptor - mus musculus expression: liver kidney brain strains: shrsp sprague_dawley wistar_kyo gbp
RATTUS01273	mwgrat10K#7225	caa03190	sequence 2 from patent wo9610636 expression: liver brain strains: sprague_dawley wistar_kyoto trembl
RATTUS01287	mwgrat10K#7238	ak011418	ak011418_1 riken full-length enriched library, clone:2610016f14 - mus musculus expression: brain strains: shrsp wistar_kyoto gbp
RATTUS01294	mwgrat10K#7245	q9nvl7	cdna flj10651 fis, clone nt2rp2005868 expression: brain strains: shrsp sprague_dawley wistar_kyoto trembl

Figure 23

Nucleotide GenBank Accession Number or Manufacturer Sequence ID	Gene Name or Manufacturer Probe Name	Protein Product GeneBank Accsssion Number or Manufacturer Sequence Reference	Description
RATTUS01392	mwgrat10K#7330	ak009373	ak009373_1 riken full-length enriched library, clone:2310015o17 - mus musculus expression: liver brain strains: sprague_dawley wistar_kyoto gbp
RATTUS01404	mwgrat10K#7342	m59288	m59288_1 ferrochelatase - mus musculus expression: liver brain strains: shrsp wistar_kyoto gbp
RATTUS01416	mwgrat10K#7352	af212995	af212995_1 cul4b cullin cul4b - homo sapiens expression: liver strains: wistar_kyoto gbp
RATTUS01422	mwgrat10K#7358	ak005698	ak005698_1 riken full-length enriched library, clone:1700007d05 - mus musculus expression: liver heart strains: sprague_dawley wistar_kyoto gbp
RATTUS01478	mwgrat10K#7409	cab69424	sequence 13 from patent wo9826065 fragment expression: liver brain strains: shrsp sprague_dawley wistar_kyoto trembl
RATTUS01526	mwgrat10K#7452	q9wuz9	nucleoside diphosphatase er-udpase expression: liver kidney strains: wistar_kyoto trembl
RATTUS01538	mwgrat10K#7464	bc012401	bc012401_1 unknown protein for mgc:11724 - mus musculus expression: liver brain strains: shrsp sprague_dawley wistar_kyoto gbp
RATTUS01590	mwgrat10K#7512	q9h9h1	cdna flj12756 fis, clone nt2rp2001295, weakly zinc/cadmium resistance protein expression: liver brain strains: sprague_dawley wistar_kyoto trembl
RATTUS01595	mwgrat10K#7517	bc003454	bc003454_1 riken cdna 1110021n07 gene - mus musculus expression: kidney heart strains: sprague_dawley wistar_kyoto gbp
RATTUS01656	mwgrat10K#7570	q9jk31	atfa-associated factor expression: heart kidney brain strains: shrsp sprague_dawley wistar_kyoto trembl
RATTUS01669	mwgrat10K#7583	bc006941	bc006941_1 sphingosine kinase 2 - mus musculus expression: kidney strains: shrsp wistar_kyoto gbp
RATTUS01679	mwgrat10K#7592	ak008666	ak008666_1 riken full-length enriched library, clone:2210008a03 - mus musculus expression: kidney strains: shrsp wistar_kyoto gr
RATTUS01713	mwgrat10K#7622	q9nqq7	ba394o2.1 cgi-15 protein expression: brain heart kidney strains: shrsp sprague_dawley wistar_kyoto trembl
RATTUS01762	mwgrat10K#7667	q9h5w6	cdna: flj22937 fis, clone kat07960 expression: liver brain kidney strains: shrsp sprague_dawley wistar_kyoto trembl.
RATTUS01834	mwgrat10K#9859	q9jmf6	fragment expression: kidney brain strains: shrsp wistar_kyoto trembl
RATTUS01846	mwgrat10K#7749	ax118871	ax118871_1 homo sapiens sequence 35 from patent wo0129221 unnamed protein product expression: kidney strains: shrsp wistar_kyoto gbp

Figure 23

Nucleotide GenBank Accession Number or Manufacturer Sequence ID	Gene Name or Manufacturer Probe Name	Protein Product GeneBank Accsssion Number or Manufacturer Sequence Reference	Description
RATTUS01882	mwgrat10K#7785	bc003936	bc003936_1 unknown protein for mgc:7327 - mus musculus expression: brain strains: shrsp sprague_dawley gbp
RATTUS02017	mwgrat10K#7912	q9qxm0	alpha/beta hydrolase-2 fold protein expression: liver strains: shrsp sprague_dawley trembl
RATTUS02037	mwgrat10K#7932	bc011313	bc011313_1 unknown protein for mgc:19443 - mus musculus expression: liver brain strains: shrsp sprague_dawley gbp
RATTUS02056	mwgrat10K#7949	q9hc79	serine kinase expression: liver brain strains: shrsp trembl
RATTUS02104	mwgrat10K#7991	aj277386	aj277386_1 p14 late endosomal/lysosomal mp1 interacting protein - mus musculus expression: brain heart strains: shrsp sprague_dawley gbp
RATTUS02120	mwgrat10K#8006	af077188	af077188_1 cul4a cullin 4a - homo sapiens expression: liver brain kidney strains: shrsp sprague_dawley gbp
RATTUS02168	mwgrat10K#8052	ak011126	ak011126_1 riken full-length enriched library, clone:2600001b17 - mus musculus expression: brain heart strains: shrsp sprague_dawley gbp
RATTUS02183	mwgrat10K#8067	o00495	26s proteasome subunit 9 expression: heart brain strains: shrsp sprague_dawley trembl
RATTUS02235	mwgrat10K#8116	x53247	x53247_1 member of ras gene family en-7 protein - mus musculus expression: kidney brain strains: sprague_dawley wistar_kyoto gbp
RATTUS02251	mwgrat10K#8130	cac24865	sequence 3 from patent wo0100831 expression: liver heart brain kidney strains: shrsp sprague_dawley wistar_kyoto tremb
RATTUS02282	mwgrat10K#8152	af104398	af104398_1 cornichon - homo sapiens expression: liver brain heart strains: shrsp sprague_dawley wistar_kyoto gbp
RATTUS02294	mwgrat10K#8162	ak014369	ak014369_1 riken full-length enriched library, clone:3300002i08 - mus musculus expression: brain heart strains: sprague_dawley wistar_kyoto gbp
RATTUS02298	mwgrat10K#8166	ak015239	ak015239_1 riken full-length enriched library, clone:4930429h24 - mus musculus expression: heart brain strains: shrsp sprague_dawley wistar_kyoto gbp
RATTUS02333	mwgrat10K#8195	q9ugg6	39k3 protein expression: heart brain strains: sprague_dawley wistar_kyoto trembl
RATTUS02339	mwgrat10K#8200	q9jkw0	arl-6 interacting protein-1 expression: liver kidney brain strains: shrsp sprague_dawley wistar_kyoto trembl
RATTUS02445	mwgrat10K#8294		expression: liver brain strains: shrsp sprague_dawley wistar_kyoto mwg own new gene sequence

Figure 23

Nucleotide GenBank Accession Number or Manufacturer Sequence ID	Gene Name or Manufacturer Probe Name	Protein Product GeneBank Accsssion Number or Manufacturer Sequence Reference	Description
RATTUS02490	mwgrat10K#8335		expression: kidney brain strains: shrsp wistar_kyoto mwg own new gene sequence
RATTUS02564	mwgrat10K#8395	q9h871	cdna fij13910 fis, clone y79aa1000131; trembl q9h6w5 cdna: fij21795 hep00531 expression: liver strains: shrsp trembl
RATTUS02579	mwgrat10K#8408	q9hbm3	dipeptidyl peptidase 8 fragment expression: liver strains: shrsp trembl
RATTUS02653	mwgrat10K#8468	bc003862	bc003862_1 transmembrane 9 superfamily member 2 - mus musculus expression: liver heart kidney brain strains: shrsp sprague_dawley wistar_kyoto gbp
RATTUS02662	mwgrat10K#8476	q14667	kiaa0100 protein expression: liver kidney heart brain strains: shrsp sprague_dawley wistar_kyoto trembl
RATTUS02688	mwgrat10K#8499	q9nsl9	hypothetical 22.2 kda protein fragment expression: brain strains: wistar_kyoto trembl
RATTUS02717	mwgrat10K#8524	af295358	af295358_1 unknown - mus musculus expression: brain strains: wistar_kyoto gbp
RATTUS02731	mwgrat10K#6250	ak017729	ak017729_1 riken full-length enriched library, clone:5730494n06 - mus musculus; wistar_kyoto trembl cac25005 sequence 49 from patent wo0100806 precursor expression: brain strains: shrsp gbp
RATTUS02792	mwgrat10K#8583	u59321	u59321_1 p72 dead-box protein p72 - homo sapiens expression: heart strains: wistar_kyoto gbp
RATTUS02814	mwgrat10K#8598	u58135	u58135_1 poly a polymerase v - mus musculus; heart trembl q9r1r3 testis-specific expression: liver kidney brain strains: shrsp wistar_kyoto gbp
RATTUS02918	mwgrat10K#8683	q92544	myeloblast kiaa0255 expression: liver strains: wistar_kyoto trembl
RATTUS02943	mwgrat10K#8699	q9h2j3	npd016 expression: liver strains: wistar_kyoto trembl
RATTUS02971	mwgrat10K#8723	bc002137	bc002137_1 cg13018 gene product - mus musculus expression: liver strains: wistar_kyoto gbp
RATTUS03203	mwgrat10K#8914	q9y6a4	transcription factor iib; trembl p70212 hypothetical 22.7 kda protein expression: liver brain strains: sprague_dawley wistar_kyoto trembl
RATTUS03223	mwgrat10K#8928	q9jil0	lmbr1 long form expression: brain strains: sprague_dawley trembl
RATTUS03260	mwgrat10K#9233	q9y449	traf4-associated factor 2 fragment; shrsp expression: brain strains: sprague_dawley trembl
RATTUS03288	mwgrat10K#8981	o15194	ya22 protein hya22; kidney wistar_kyoto expression: brain strains: sprague_dawley trembl
RATTUS03326	mwgrat10K#9012	bc007154	bc007154_1 unknown protein for image:3485091 - mus musculus expression: brain strains: sprague_dawley gbp

Figure 23

Nucleotide GenBank Accession Number or Manufacturer Sequence ID	Gene Name or Manufacturer Probe Name	Protein Product GeneBank Accsssion Number or Manufacturer Sequence Reference	Description
RATTUS03387	mwgrat10K#9060	ak003050	ak003050_1 riken full-length enriched library, clone:0710008m05 - mus musculus expression: heart strains: sprague_dawley gbp
RATTUS03472	mwgrat10K#9126	u62325	u62325_1 hfe65l fe65-like protein - homo sapiens expression: heart strains: sprague_dawley gbp
RATTUS03489	mwgrat10K#9139	q9nt50	hypothetical 28.7 kda protein fragment expression: liver strains: sprague_dawley trembl
RATTUS03495	mwgrat10K#9144	q9wuz9	nucleoside diphosphatase er-udpase expression: liver strains: sprague_dawley trembl
RATTUS03510	mwgrat10K#9158	o75071	kiaa0494 protein expression: liver strains: sprague_dawley trembl
RATTUS03523	mwgrat10K#9169	al356440	al356440_1 dj299f11.1 dj299f11.1 d.melanogaster protein cg14464 - homo sapiens expression: liver strains: sprague_dawley gbp
RATTUS03577	mwgrat10K#9213	o35963	rab33b expression: brain strains: shrsp trembl
RATTUS03642	mwgrat10K#9265	cac09285	sequence 1 from patent wo9814562 fragment expression: brain strains: shrsp trembl
RATTUS03669	mwgrat10K#9288	bc009494	bc009494_1 unknown protein for mgc:16403 - homo sapiens expression: brain strains: shrsp gbp
RATTUS03700	mwgrat10K#9318	q9nql3	ba11d8.1 yeast ubiquitin conjugating enzyme ubc6 homolog fragment expression: brain strains: shrsp trembl
RATTUS03772	mwgrat10K#6932	u95498	u95498_1 af1q - mus musculus expression: brain strains: shrsp sprague_dawley wistar_kyoto gbp
RATTUS03793	mwgrat10K#9398	o75061	kiaa0473 protein expression: brain strains: shrsp trembl
RATTUS03819	mwgrat10K#9421	o75061	kiaa0473 protein expression: brain strains: shrsp trembl
RATTUS03860	mwgrat10K#9455	q9y4c4	masl1 protein expression: heart strains: shrsp trembl
RATTUS03893	mwgrat10K#9483	q9jjr5	c11orf17 protein expression: heart strains: shrsp trembl
RATTUS03951	mwgrat10K#9525	o00495	26s proteasome subunit 9 expression: heart strains: shrsp trembl
RATTUS03971	mwgrat10K#9537	x61585	x61585_1 polynucleotide adenylyltransferase - bos taurus expression: liver heart kidney strains: shrsp wistar_kyoto gbp
RATTUS04030	mwgrat10K#9583	bc002867	bc002867_1 unknown protein for image:3940519 - homo sapiens expression: kidney strains: shrsp gbp
RATTUS04036	mwgrat10K#9589	bc013036	bc013036_1 unknown protein for mgc:4734 - homo sapiens expression: kidney strains: shrsp gbp
RATTUS04052	mwgrat10K#9603	q9h4p0	clone cdabp0035 sequence expression: kidney strains: shrsp trembl
RATTUS04155	mwgrat10K#9696		expression: heart strains: sprague_dawley mwg own new gene sequence

Figure 23

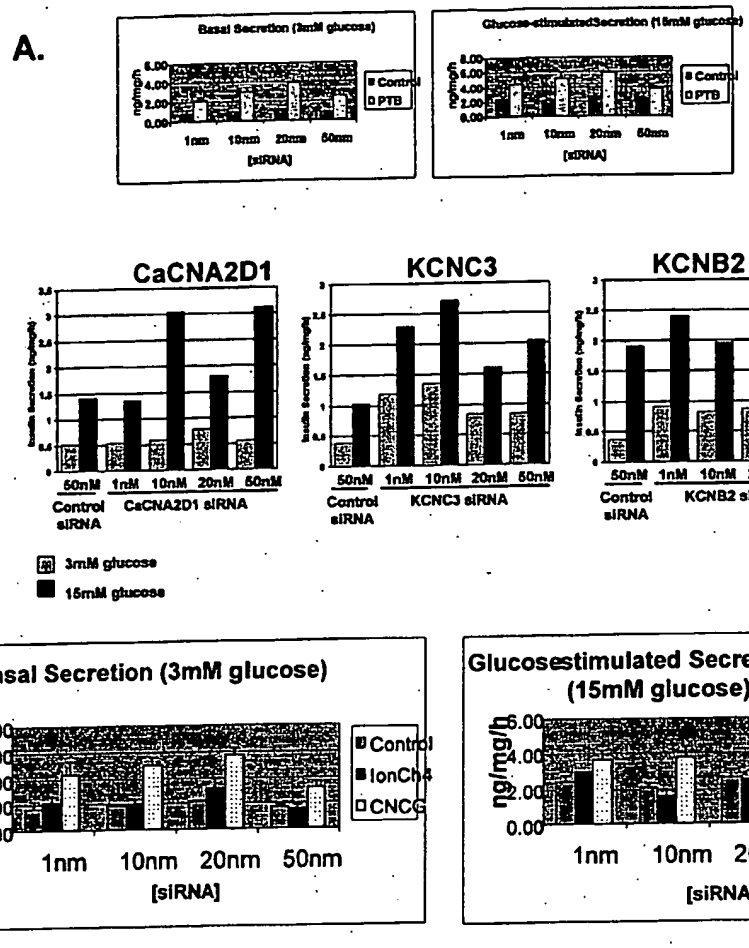


Figure 24

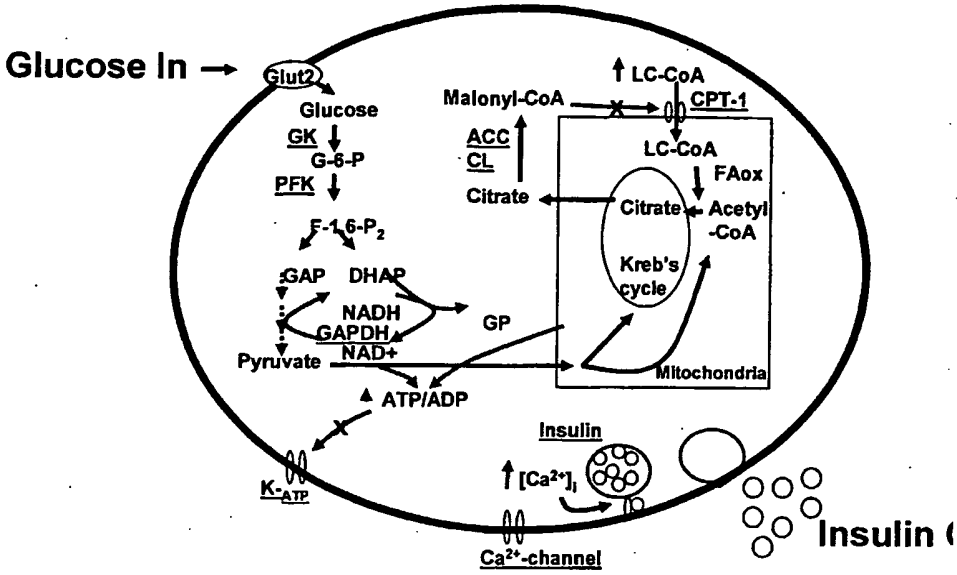

Glucose In
Glut2
Glucose
GK
G-6-P
PFK
F-1,6-P2
GAP
DHAP
NADH
GAPDH
NAD+
Pyruvate
GP
ATP/ADP
K-ATP
Malonyl-CoA
ACC
CL
Citrate
LC-CoA
CPT-1
LC-CoA
FAox
Citrate
Acetyl
-CoA
Kreb's
cycle
Mitochondria
Insulin
[Ca2+]i
Ca2+-channel
Insulin

Figure 25

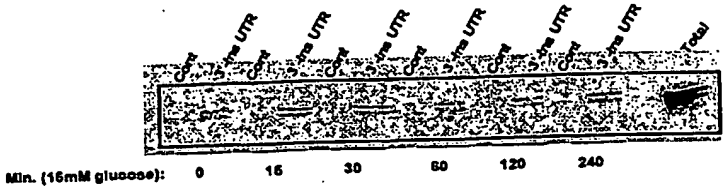


Fig. 6A

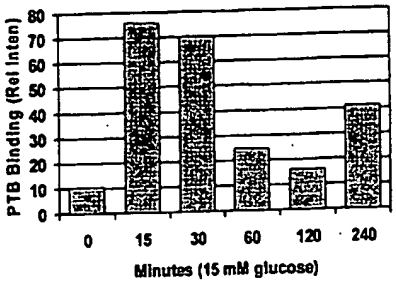


Fig. 6B

Nucleotide GenBank Accession Number or Manufacturer Sequence ID	Gene Name or Manufacturer Probe Name	Protein Product GeneBank Accsssion Number or Manufacturer Sequence Reference	Kinases
NM_031081	Pdpk1	NP_112343	Rattus norvegicus 3-phosphoinositide dependent protein kinase-1 (Pdpk1), mRNA.
NM_022799	Nucks	NP_073636	Rattus norvegicus nuclear ubiquitous casein kinase 2 (Nucks), mRNA.
NM_019248	Ntrk3	NP_062121	Rattus norvegicus neural receptor protein-tyrosine kinase (Ntrk3), mRNA.
NM_053585	Madd	NP_446037	Rattus norvegicus MAP-kinase activating death domain (Madd), mRNA.
NM_022627	Prkab2	NP_072149	Rattus norvegicus AMP-activated protein kinase beta-2 regulatory subunit (Prkab2), mRNA.
NM_012727	Camk4	NP_036859	Rattus norvegicus calcium/calmodulin-dependent protein kinase IV (Camk4), mRNA.
NM_012713	Prkcb1	NP_036845	Rattus norvegicus protein kinase C, beta 1 (Prkcb1), mRNA.
NM_013218	Ak3	NP_037350	Rattus norvegicus adenylate kinase 3 (Ak3), mRNA.
NM_017246	Map2k5	NP_058942	Rattus norvegicus mitogen activated protein kinase kinase 5 (Map2k5), mRNA.
AB040531	RH2K	BAA96496	Rattus norvegicus mRNA for RH2K2, complete cds.
U39572		AAD10400	Rattus norvegicus phosphatidylinositol 4-kinase mRNA, complete cds.
NM_012565	Gck	NP_036697	Rattus norvegicus glucokinase (Gck), mRNA.
NM_032080	Gsk3b	NP_114469	Rattus norvegicus glycogen synthase kinase 3 beta (Gsk3b), mRNA.
NM_080584	Phkg2	NP_542151	Rattus norvegicus phosphorylase kinase, gamma 2 (testis) (Phkg2), mRNA.

Nucleotide GenBank Accession Number or Manufacturer Sequence ID	Gene Name or Manufacturer Probe Name	Protein Product GeneBank Accsssion Number or Manufacturer Sequence Reference	Phosphatases
NM_012637	Ptpn1	NP_036769	Rattus norvegicus protein tyrosine phosphatase, non-receptor type 1 (Ptpn1), mRNA.
NM_019253	Ptpn5	NP_062126	Rattus norvegicus protein tyrosine phosphatase, non-receptor type 5 (Ptpn5), mRNA.
NM_019214	Inpp5d	NP_062184	Rattus norvegicus inositol polyphosphate-5-phosphatase D (Inpp5d), mRNA

Figure 27

NM_013080	Ptprz1	NP_037212	Rattus norvegicus protein tyrosine phosphatase, receptor-type, Z polypeptide 1 (Ptprz1), mRNA.
NM_053883	Dusp6	NP_446335	Rattus norvegicus dual specificity phosphatase 6 (Dusp6), mRNA.
NM_057115	Ptpn12	NP_476456	Rattus norvegicus protein tyrosine phosphatase, non-receptor type 12 (Ptpn12), mRNA.
NM_013098	G6pc	NP_037230	Rattus norvegicus glucose-6-phosphatase, catalytic (G6pc), mRNA.
AB040531	RH2K	BAA96496	Rattus norvegicus mRNA for RH2K2, complete cds.

Nucleotide GenBank Accession Number or Manufacturer Sequence ID	Gene Name or Manufacturer Probe Name	Protein Product GeneBank Accsssion Number or Manufacturer Sequence Reference	Ion Channels/Regulators of Ion channels
AF013598		AAB69328	Rattus norvegicus proton gated cation channel DRASIC mRNA, complete cds.
NM_031548	Scnn1a	NP_113736	Rattus norvegicus sodium channel, nonvoltage-gated, type I, alpha polypeptide (Scnn1a), mRNA.
NM_012919	Cacna2d1	NP_037051	Rattus norvegicus calcium channel, voltage-dependent, alpha2/delta subunit 1 (Cacna2d1), mRNA.
NM_013192	Kcnj6	NP_037324	Rattus norvegicus potassium inwardly-rectifying channel, subfamily J, member 6 (Kcnj6), mRNA.
U78090		AAC34249	Rattus norvegicus potassium channel regulator 1 mRNA, complete cds.
AF290212		AAG35186	Rattus norvegicus calcium channel alpha-1-G subunit mRNA, complete cds.
NM_053497	Cncg	NP_445949	Rattus norvegicus cyclic nucleotide-gated cation channel (Cncg), mRNA.
Y14635		CAA74979	Rattus norvegicus mRNA for proton-gated cation channels modulatory subunit.
AJ003065		CAA05839	Rattus norvegicus mRNA for Kir2.4, inwardly rectifying potassium channel.
NM_031828	Kcnma1	NP_114016	Rattus norvegicus potassium large conductance calcium-activated channel, subfamily M, alpha member 1 (Kcnma1), mRNA.
NM_054000	Kcnb2	NP_446452	Rattus norvegicus potassium voltage gated channel, Shab-related subfamily, member 2 (Kcnb2), mRNA.
NM_021853	Slack	NP_068625	Rattus norvegicus potassium channel subunit (Slack) (Slack), mRNA.
NM_019313	Kcnn1	NP_062186	Rattus norvegicus potassium intermediate/small conductance calcium-activated channel, subfamily N, member 1 (Kcnn1), mRNA.
NM_013125	Scn5a	NP_037257	Rattus norvegicus sodium channel, voltage-gated, type V, alpha polypeptide (Scn5a), mRNA.
AJ309926	asic 1b	CAC44267	Rattus norvegicus mRNA for ion channel (asic 1b gene).
NM_053806	Kcnk6	NP_446258	Rattus norvegicus potassium channel, subfamily K, member 6 (TWIK-2) (Kcnk6), mRNA.

Figure 27

Nucleotide GenBank Accession Number or Manufacturer Sequence ID	Gene Name or Manufacturer Probe Name	Protein Product GeneBank Accsssion Number or Manufacturer Sequence Reference	Transporters
AB023645	ccc6	BAB40440	Rattus norvegicus ccc6 mRNA for cation-chloride cotransporter 6, complete cds.
AF239262	oatpE	AAK30042	Rattus norvegicus organic anion transporter E (oatpE) mRNA, complete cds.
AF273024		AAF81796	Rattus norvegicus amino acid system A transporter mRNA, complete cds.
AB000280	PHT1	BAA20489	Rattus norvegicus mRNA for peptide/histidine transporter, complete cds.
NM_017348	CHOT1	NP_059044	Rattus norvegicus choline transporter (CHOT1), mRNA.
AF268030		AAF72546	Rattus norvegicus copper transporter 1 mRNA, complete cds.
NM_022866	Slc13a3	NP_074057	Rattus norvegicus solute carrier family 13 (sodium-dependent dicarboxylate transporter), member 3 (Slc13a3), mRNA
AJ315643	Hmit	CAC51117	Rattus norvegicus mRNA for proton myo-inositol symporter (Hmit gene).
U55816	KCC2	AAC52635	Rattus norvegicus furosemide-sensitive K-Cl cotransporter (KCC2) mRNA, complete cds.
NM_013034	Slc6a4	NP_037166	Rattus norvegicus solute carrier family 6, member 4 (Slc6a4), mRNA.
NM_012879	Slc2a2	NP_037011	Rattus norvegicus solute carrier family 2, member 2 (Slc2a2), mRNA.

Nucleotide GenBank Accession Number or Manufacturer Sequence ID	Gene Name or Manufacturer Probe Name	Protein Product GeneBank Accsssion Number or Manufacturer Sequence Reference	Proteases\Peptidases
NM_012836	Cpd	NP_036968	Rattus norvegicus carboxypeptidase D (Cpd), mRNA.
AF202454		AAF17575	Rattus norvegicus testis ubiquitin specific processing protease mRNA, complete cds.
NM_017145	Mcpt1	NP_058841	Rattus norvegicus mast cell protease 1 (Mcpt1), mRNA.

Figure 27

Nucleotide GenBank Accession Number or Manufacturer Sequence ID	Gene Name or Manufacturer Probe Name	Protein Product GeneBank Accsssion Number or Manufacturer Sequence Reference	Receptors
NM_019246	Pcsk7	NP_062119	Rattus norvegicus proprotein convertase subtilisin / kexin, type 7 (Pcsk7), mRNA.
NM_017138	Lamr1	NP_058834	Rattus norvegicus laminin receptor 1 (67kD, ribosomal protein SA) (Lamr1), mRNA.
NM_012637	Ptpn1	NP_036769	Rattus norvegicus protein tyrosine phosphatase, non-receptor type 1 (Ptpn1), mRNA.
NM_016996	Casr	NP_058692	Rattus norvegicus calcium-sensing receptor (Casr), mRNA.
NM_019248	Ntrk3	NP_062121	Rattus norvegicus neural receptor protein-tyrosine kinase (Ntrk3), mRNA.
U47331		AAA88788	Rattus norvegicus metabotropic glutamate receptor 4b mRNA, complete cds.
NM_019328	Nr4a2	NP_062201	Rattus norvegicus nuclear receptor subfamily 4, group A, member 2 (Nr4a2), mRNA.
NM_012869	Npy5r	NP_037001	Rattus norvegicus neuropeptide Y receptor Y5 (Npy5r), mRNA.
NM_019253	Ptpn5	NP_062126	Rattus norvegicus protein tyrosine phosphatase, non-receptor type 5 (Ptpn5), mRNA.
NM_052807	Igf1r	NP_434694	Rattus norvegicus insulin-like growth factor 1 receptor (Igf1r), mRNA.
NM_013080	Ptprz1	NP_037212	Rattus norvegicus protein tyrosine phosphatase, receptor-type, Z polypeptide 1 (Ptprz1), mRNA.
NM_031628	Nr4a3	NP_113816	Rattus norvegicus nuclear receptor subfamily 4, group A, member 3 (Nr4a3), transcript variant 1, mRNA.
NM_017011	Grm1	NP_058707	Rattus norvegicus glutamate receptor, metabotropic 1 (Grm1), mRNA.
NM_013091	Tnfrsf1a	NP_037223	Rattus norvegicus tumor necrosis factor receptor superfamily, member 1a (Tnfrsf1a), mRNA.
NM_017071	Insr	NP_058767	Rattus norvegicus insulin receptor (Insr), mRNA.
AF161588	Gabarap	AAD47643	Rattus norvegicus GABA-A receptor-associated protein (Gabarap) mRNA, complete cds.
NM_057115	Ptpn12	NP_476456	Rattus norvegicus protein tyrosine phosphatase, non-receptor type 12 (Ptpn12), mRNA.
NM_012528	Chrnb1	NP_036660	Rattus norvegicus cholinergic receptor, nicotinic, beta polypeptide 1 (Chrnb1), mRNA.
AF010293	U131	AAB66333	Rattus norvegicus olfactory receptor (U131) mRNA, complete cds.
NM_012957	Gabrb2	NP_037089	Rattus norvegicus gamma-aminobutyric acid receptor, subunit beta 2 (Gabrb2), mRNA.
NM_012959	Gfra1	NP_037091	Rattus norvegicus glial cell line derived neurotrophic factor family receptor alpha 1 (Gfra1), mRNA.
NM_053296	Glrb	NP_445748	Rattus norvegicus glycine receptor, beta subunit (Glrb), mRNA.
AF205193		AAF19028	Rattus norvegicus glutamate receptor interacting protein 2 mRNA, complete cds.
Z23272		CAA80810	R.norvegicus PACAP receptor, hip-hop1 splice variant, complete CDS.
AF230645		AAF36975	Rattus norvegicus testis-type galactosyl receptor mRNA, complete cds.

Figure 27

NM_012896	Adora3	NP_037028	Rattus norvegicus adenosine A3 receptor (Adora3), mRNA.
NM_024146	Fgfr1	NP_077060	Rattus norvegicus Fibroblast growth factor receptor 1 (Fgfr1), mRNA.
NM_022186	Nrbf2	NP_071522	Rattus norvegicus nuclear receptor binding factor 2 (Nrbf2), mRNA.
U22830		AAA91303	Rattus norvegicus P2Y purinoceptor mRNA, complete cds.
NM_021745	Nr1h4	NP_068513	Rattus norvegicus nuclear receptor subfamily 1, group H, member 4 (Nr1h4), mRNA.
NM_013124	Pparg	NP_037256	Rattus norvegicus peroxisome proliferator activated receptor, gamma (Pparg), mRNA.
AJ011370	5-HT4	CAA09599	Rattus norvegicus mRNA for serotonin 4 receptor, splice variant r5-HT4(e).
AF016387	RXRgamma	AAD01591	Rattus norvegicus retinoid X receptor gamma (RXRgamma) mRNA, partial cds.
NM_022212	Insrr	NP_071548	Rattus norvegicus insulin receptor-related receptor (Insrr), mRNA.

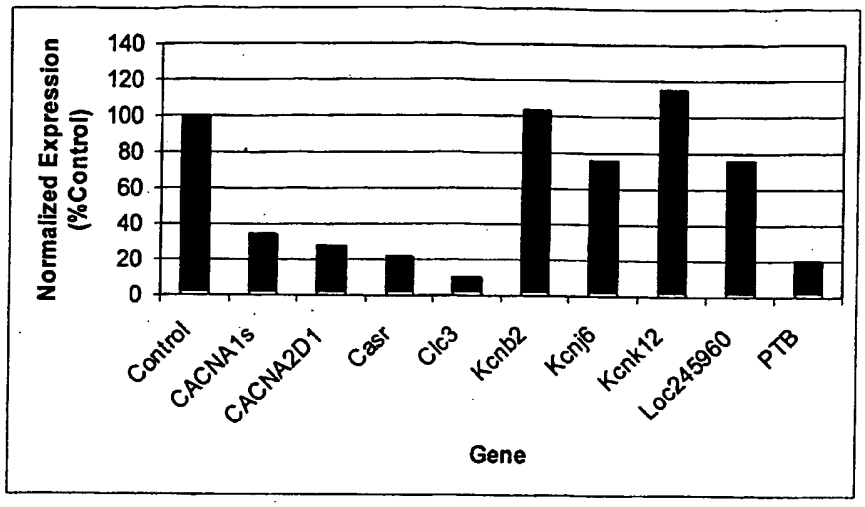
Nucleotide GenBank Accession Number or Manufacturer Sequence ID	Gene Name or Manufacturer Probe Name	Protein Product GeneBank Accsssion Number or Manufacturer Sequence Reference	Transferases
NM_022635	Cml4	NP_072157	Rattus norvegicus putative N-acetyltransferase Camello 4 (Cml4), mRNA.
NM_022280	Lrat	NP_071616	Rattus norvegicus lecithin-retinol acyltransferase (Lrat), mRNA.
X14211		CAA32428	Rat mRNA for phenylethanolamine-N-methyltransferase (PNMT).
NM_031635	Fut2	NP_113823	Rattus norvegicus fucosyltransferase 2 (Fut2), mRNA.
NM_013029	Siat8c	NP_037161	Rattus norvegicus sialyltransferase 8 C (Siat8c), mRNA.
NM_031980	Ugt2b12	NP_114186	Rattus norvegicus UDP-glucuronosyltransferase (Ugt2b12), mRNA.
NM_022219	Fut4	NP_071555	Rattus norvegicus alpha 1,3-fucosyltransferase Fuc-T (similar to mouse Fut4) (Fut4), mRNA.
NM_053437	Dgat1	NP_445889	Rattus norvegicus diacylglycerol O-acyltransferase 1 (Dgat1), mRNA.

Figure 27

Nucleotide GenBank Accession Number or Manufacturer Sequence ID	Gene Name or Manufacturer Probe Name	Protein Product GeneBank Accsssion Number or Manufacturer Sequence Reference	Transcription Factors
NM_012747	Stat3	NP_036879	Rattus norvegicus signal transducer and activator of transcription 3 (Stat3), mRNA.
NM_017339	Isl1	NP_059035	Rattus norvegicus ISL1 transcription factor, LIM/homeodomain 1 (Isl1), mRNA.
NM_021770	Olig1	NP_068538	Rattus norvegicus oligodendrocyte transcription factor 1 (Olig1), mRNA.

Figure 27

A.



B.

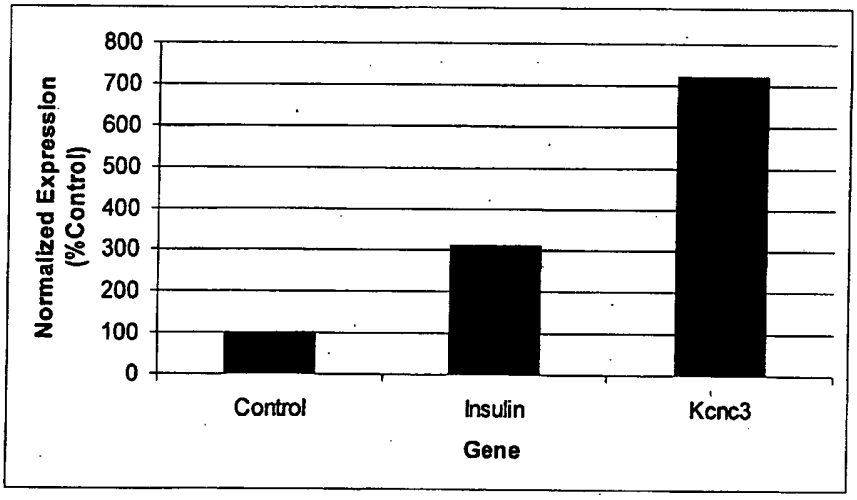


Figure 28

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(71) Applicant *(for all designated States except US)*: **RIBONOMICS INC.** [US/US]; 3908 Patriot Drive, Durham, NC 27703 (US).

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(74) Agent: **STEEL, Diana, M.**; Testa, Hurwitz & Thibeault, LLP, High Street Tower, 125 High Street, Boston, MA 02110 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
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(88) Date of publication of the international search report:
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: METHODS FOR IDENTIFYING THERAPEUTIC TARGETS INVOLVED IN GLUCOSE AND LIPID METABOLISM

(57) Abstract: The identification and evaluation of mRNA and protein targets associated with RNA binding proteins or mRNP complexes is described. In particular, the invention provides methods for identifying RNA binding proteins associated with physiological pathways that participate in glucose and lipid metabolism and mRNAs that exhibit coordinated gene regulation across thoseMpathways. Candidate targets are provided that are useful for the diagnosis or treatment of diseases related to diseases, such as disease related to aberrant glucose and lipid metabolism, such as, for example, obesity, diabetes, and hypoglycemia.

WO 2004/092740 A3

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2004/010686

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G01N33/68 G01N33/53

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 G01N C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PHELPS W. B.: "Innovative Systems Biology"'Online! 6 November 2002 (2002-11-06), XP002291620 Retrieved from the Internet: URL:http://www.ribonomics.com/news/presentations/ribonomics_RNA_in_Drug_Development.pdf> 'retrieved on 2004-08-05!	1-11,14, 15, 18-20, 30,37
Y	the whole document	12
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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"P" document published prior to the international filing date but later than the priority date claimed

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Date of the actual completion of the international search	Date of mailing of the international search report
27 October 2004	04.01.05

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Rutz, B

Form PCT/ISA/210 (second sheet) (January 2004)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	TILLMAR LINDA ET AL: "Hypoxia may increase rat insulin mRNA levels by promoting binding of the polypyrimidine tract-binding protein (PTB) to the pyrimidine-rich insulin mRNA 3'-untranslated region." MOLECULAR MEDICINE (CAMBRIDGE, MASS.) MAY 2002, vol. 8, no. 5, May 2002 (2002-05), pages 263-272, XP002291619 ISSN: 1076-1551	31-33
Y	the whole document	12
X	CHEATHAM B. ET AL.: "A ribonomic analysis of adipocytes: a systems biology tool"'Online! 2 December 2002 (2002-12-02), XP002291621 Retrieved from the Internet: URL:http://www.ribonomics.com/news/presentations/ribonomics_MetabolicDisease2002Poster.pdf> 'retrieved on 2004-08-05! the whole document	1-11,14, 15, 18-20, 25-30,37
X	US 2002/004211 A1 (TENENBAUM SCOTT A ET AL) 10 January 2002 (2002-01-10) paragraph '0004!; figures 2,4,8; table 1 paragraph '0019! paragraph '0049! paragraph '0064! paragraph '0072! - paragraph '0074!	1,6,7, 9-12,14, 20-29
X	CEMAN S ET AL: "Isolation of an FMRP-associated messenger ribonucleoprotein particle and identification of nucleolin and the fragile X-related proteins as components of the complex." MOLECULAR AND CELLULAR BIOLOGY. DEC 1999, vol. 19, no. 12, December 1999 (1999-12), pages 7925-7932, XP002302896 ISSN: 0270-7306 the whole document	21-24

-/--

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	OHASHI SACHIYO ET AL: "Identification of mRNA/protein (mRNP) complexes containing Puralpha, mStaufen, fragile X protein, and myosin Va and their association with rough endoplasmic reticulum equipped with a kinesin motor." THE JOURNAL OF BIOLOGICAL CHEMISTRY. 4 OCT 2002, vol. 277, no. 40, 4 October 2002 (2002-10-04), pages 37804-37810, XP002302897 ISSN: 0021-9258 the whole document	21-24
X	TENENBAUM SCOTT A ET AL: "Ribonomics: Identifying mRNA subsets in mRNP complexes using antibodies to RNA-binding proteins and genomic arrays" METHODS (ORLANDO), vol. 26, no. 2, February 2002 (2002-02), pages 191-198, XP002291623 ISSN: 1046-2023 page 194, right-hand column, line 12 - page 195, left-hand column, paragraph 1	21-24
X	GAVIN A-C ET AL: "Functional organization of the yeast proteome by systematic analysis of protein complexes" NATURE, MACMILLAN JOURNALS LTD. LONDON, GB, vol. 415, January 2002 (2002-01), pages 141-147, XP002958851 ISSN: 0028-0836 page 143, right-hand column, last paragraph - page 144, left-hand column, paragraph 1; figure 3	21-24
X	TILLMAR LINDA ET AL: "Control of insulin mRNA stability in rat pancreatic islets. Regulatory role of a 3'-untranslated region pyrimidine-rich sequence." THE JOURNAL OF BIOLOGICAL CHEMISTRY. 11 JAN 2002, vol. 277, no. 2, 11 January 2002 (2002-01-11), pages 1099-1106, XP002302898 ISSN: 0021-9258	31-33
Y	the whole document	35,36

-/--

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HIERONYMUS HALEY ET AL: "Genome-wide analysis of RNA-protein interactions illustrates specificity of the mRNA export machinery." NATURE GENETICS. FEB 2003, vol. 33, no. 2, February 2003 (2003-02), pages 155-161, XP002302899 ISSN: 1061-4036	34
Y	the whole document	35,36
X	LELIVELT M J ET AL: "Yeast Upf proteins required for RNA surveillance affect global expression of the yeast transcriptome" MOLECULAR AND CELLULAR BIOLOGY, AMERICAN SOCIETY FOR MICROBIOLOGY, WASHINGTON, US, vol. 19, no. 10, October 1999 (1999-10), pages 6710-6719, XP002977598 ISSN: 0270-7306 the whole document	34
A	RIBONOMICS INC.: "Research & Technology"'Online! 17 March 2003 (2003-03-17), XP002291622 Retrieved from the Internet: URL:http://web.archive.org/web/20030317064208/http://www.ribonomics.com/technology/index.html> 'retrieved on 2004-08-05!	
A	TENENBAUM S A: "IDENTIFYING MRNA SUBSETS IN MESSENGER RIBONUCLEOPROTEIN COMPLEXES BY USING CDNA ARRAYS" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, NATIONAL ACADEMY OF SCIENCE. WASHINGTON, US, vol. 97, no. 26, 19 December 2000 (2000-12-19), pages 14085-14090, XP000995310 ISSN: 0027-8424	
A	KEENE JACK D: "Ribonucleoprotein infrastructure regulating the flow of genetic information between the genome and the proteome" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, vol. 98, no. 13, 19 June 2001 (2001-06-19), pages 7018-7024, XP002291624 ISSN: 0027-8424	

-/--

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	KEENE JACK D ET AL: "Eukaryotic mRNPs may represent posttranscriptional operons" MOLECULAR CELL, vol. 9, no. 6, June 2002 (2002-06), pages 1161-1167, XP002291625 ISSN: 1097-2765	
A	RODGERS NANCY D ET AL: "Identifying mRNAs bound by RNA-binding proteins using affinity purification and differential display." METHODS (SAN DIEGO, CALIF.) FEB 2002, vol. 26, no. 2, February 2002 (2002-02), pages 115-122, XP002291626 ISSN: 1046-2023	
A	BROWN V ET AL: "Microarray identification of FMRP-associated brain mRNAs and altered mRNA translational profiles in fragile X syndrome." CELL. 16 NOV 2001, vol. 107, no. 4, 16 November 2001 (2001-11-16), pages 477-487, XP002291627 ISSN: 0092-8674	
P,X	KNOCH KLAUS-PETER ET AL: "Polypyrimidine tract-binding protein promotes insulin secretory granule biogenesis." NATURE CELL BIOLOGY. MAR 2004, vol. 6, no. 3, March 2004 (2004-03), pages 207-214, XP002302900 ISSN: 1465-7392 the whole document	31,33
P,X	HEROLD ANDREA ET AL: "Genome-wide analysis of nuclear mRNA export pathways in Drosophila." THE EMBO JOURNAL. 15 MAY 2003, vol. 22, no. 10, 15 May 2003 (2003-05-15), pages 2472-2483, XP002302901 ISSN: 0261-4189 the whole document	34

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2004/010686

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-20,25-30,37

   screening methods involving the comparison of RNA or protein levels of at least one component of an isolated mRNP from two different cellular phenotypes or states (e.g. treated vs. untreated)

   ---

2. claims: 21-24

   method for identifiying a gene or gene product involved in a physiological pathway by isolating additional components of an mRNP complex that contains a component already known to be involved in said pathway

   ---

3. claims: 31,32

   method for identifying an insulin production regulating protein agent characterized by its ability to bind to the 3' or 5' untranslated region of a preproinsulin mRNA

   ---

4. claim: 33

   mRNP complex involved in glucose or lipid metabolism which comprises PTB protein and an mRNA associated with PTB

   ---

5. claims: 34-36

   method for identifying a component of an mRNP complex by expression profiling of RNA with or without prior inhibition of expression of an RNA binding protein

   ---

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US2004/010686

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2002004211 A1	10-01-2002	US 2003235830 A1	25-12-2003
		US 2003211466 A1	13-11-2003
		US 2004096878 A1	20-05-2004
		AU 2743101 A	09-07-2001
		CA 2396058 A1	05-07-2001
		EP 1254370 A1	06-11-2002
		JP 2004520002 T	08-07-2004
		WO 0148480 A1	05-07-2001